Mechanical Ventilation from Pathophysiology to Clinical Evidence

Giacomo Bellani
Editor

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Editor
Giacomo Bellani
School of Medicine and Surgery
University of Milano-Bicocca
Monza, Italy

Department of Emergency and Intensive Care
ASST Monza, San Gerardo Hospital
Monza, Italy

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Foreword

Writing a few words of introduction for this new book *Mechanical Ventilation: from Pathophysiology to Clinical Evidence* is an opportunity to stress the fact that Mechanical Ventilation still is the most widely applied life support technique in the care of the Critically Ill Patient.

Millions of people, every year, owe indeed their survival to Mechanical Ventilation.

In 1952, thanks to the physiological approach of Dr. Bjorn A Ibsen, it warranted the necessary ventilatory support to children affected by poliomyelitis. From then on, it has developed from a simple technique to a sophisticated clinical science; as such it requires a solid knowledge of pathophysiological principles, a familiarity with the technology and the devices involved, and a deep clinical background, extending well beyond the respiratory system.

Starting with the Polio epidemic in Copenhagen, through the most recent H1N1 influenza and the latest COVID-19 pandemic, Mechanical Ventilation has proven the single most important vital support in epidemic situation, and a fundamental backbone of the critical care approach.

This book endeavors to cover systematically the vast clinical science of Mechanical Ventilation, from Pathophysiology to Clinical Evidence, as its title says. It addresses mainly the field of Critical Care, moving from the basic technical background to pathophysiological monitoring, up to the real life of clinical scenarios.

This rather original approach provides an effective guide to the topic, providing a critical update of the science of Mechanical Ventilation.

A most impressive team of authors generated this book, bound to become a most important reference for anyone interested in this discipline.

I congratulate the Editor, Giacomo Bellani, and all the authors, for their achievement.

Antonio Pesenti
Department of Anesthesia and Critical Care
Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico
Milan
Italy

Department of Pathophysiology and Transplantation
Università degli Studi di Milano
Milan
Italy

Preface

I was asked many times what brought me to the decision of realizing a book on Mechanical Ventilation. And the answer, such as the idea underpinning this book, is rather simple: I am strongly convinced that, in clinical practice, while guidelines are necessary, and protocols might be useful, mechanical ventilation cannot be managed optimally unless clinicians have proper knowledge and understanding of physiology (which during disease becomes "pathophysiology") of the respiratory system–ventilator complex. From pathophysiology stem the concepts that are tested in clinical trials and are incorporated in guidelines.

Moreover, several papers open with a sentence that sounds like "Mechanical Ventilation is a life-saving treatment for acute respiratory failure….." And this is certainly the case. However, what I find almost unique to mechanical ventilation is that it gives a unique opportunity to understand the disease of our patients and to monitor in real time the response to clinical interventions. Just by looking at a waveform and measuring a few parameters, we may judge if increasing PEEP led to overdistension, if a bronchodilator we just introduced is working or not, if patient is receiving too much assistance from the ventilator or too little, if patients fail weaning due to muscle weakness, only to quote a few examples. Hence, Mechanical Ventilation is, indeed, also a diagnostic tool (often in real time). This is especially important in an era of personalized medicine: guidelines and protocols—while undoubtedly useful—will never have the granularity nor will be able to integrate all the complex information required to treat a specific patient. Optimizing the patient–ventilator interaction to achieve the best possible outcomes is personalized medicine at the bedside. Again, only understanding pathophysiology will be a crucial tool to achieve this goal.

I must also say that, overall, the book definitely exceeds my expectations. I have had the privilege, over the years, to meet many colleagues who are real experts on the topics. By reading their papers and listening to their talks, it is clear that their knowledge comes also from everyday practice and experience. I was proud and honored when they accepted to collaborate in this project, and they have all provided extremely high-quality chapters. It is important to know that I asked the authors to limit the number of references: rather than a fully exhaustive literature overview, I felt more useful to point the readers toward the resources who the authors judged more useful. Hence if some relevant reference is missing, no blame on the authors.

I sincerely hope that this book will help our (especially younger) colleagues not simply to "learn" and, most importantly, to "understand" Mechanical Ventilation but also to be "captured" by it, so to be in the position of developing and testing novel ideas and/or become teacher to others.

Monza, Italy Giacomo Bellani

Contents

Part I

Techniques

Basic Physiology of Respiratory System: Gas Exchange and Respiratory Mechanics

1

Khoi Do and Guido Musch

1.1 Gas Exchange

Gas exchange is the process by which atmospheric oxygen (O_2) is transferred from the alveolar gas into the bloodstream and carbon dioxide (CO_2) from the bloodstream into the alveolar gas phase. CO_2 is then eliminated into the atmosphere by ventilation. Gas exchange occurs at the level of the transitional and respiratory zones of the respiratory system, which are areas of the lung lined by alveoli. Alveoli are tiny air sacs encased in capillary beds (Fig. 1.1). The proximity between air and blood in the alveoli creates an optimal environment for gas exchange. O_2 and CO_2 are brought to the site of gas exchange by ventilation and perfusion, respectively, and their transfer across the air-blood interface (i.e., alveolo-capillary membrane) is driven by simple diffusion down partial pressure gradients [1]. In this section, we discuss the individual components of gas exchange: delivery of O_2, removal of CO_2, ventilation-to-perfusion matching, and gas diffusion.

Atmospheric oxygen is delivered to the alveoli by ventilation. The primary determinant of the amount of O_2 delivered to the alveoli is the fraction of inspired O_2. This is best appreciated through the alveolar gas equation where P_AO_2 = partial pressure of alveolar O_2, P_{atm} = atmospheric barometric pressure, P_{H_2O} = partial pressure of water vapor at body temperature, F_IO_2 = fraction of inspired O_2, P_ACO_2 = partial pressure of alveolar CO_2, and R = ratio of CO_2 entering to O_2 leaving alveolar gas (i.e., respiratory quotient) [1, 2].

$$P_AO_2 = \left[\left(P_{atm} - P_{H_2O}\right) \times F_IO_2\right] - \left(\frac{P_ACO_2}{R}\right)$$

K. Do · G. Musch (✉)
Department of Anesthesiology and Perioperative Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA
e-mail: khoi.do@umassmed.edu; guido.musch@umassmed.edu

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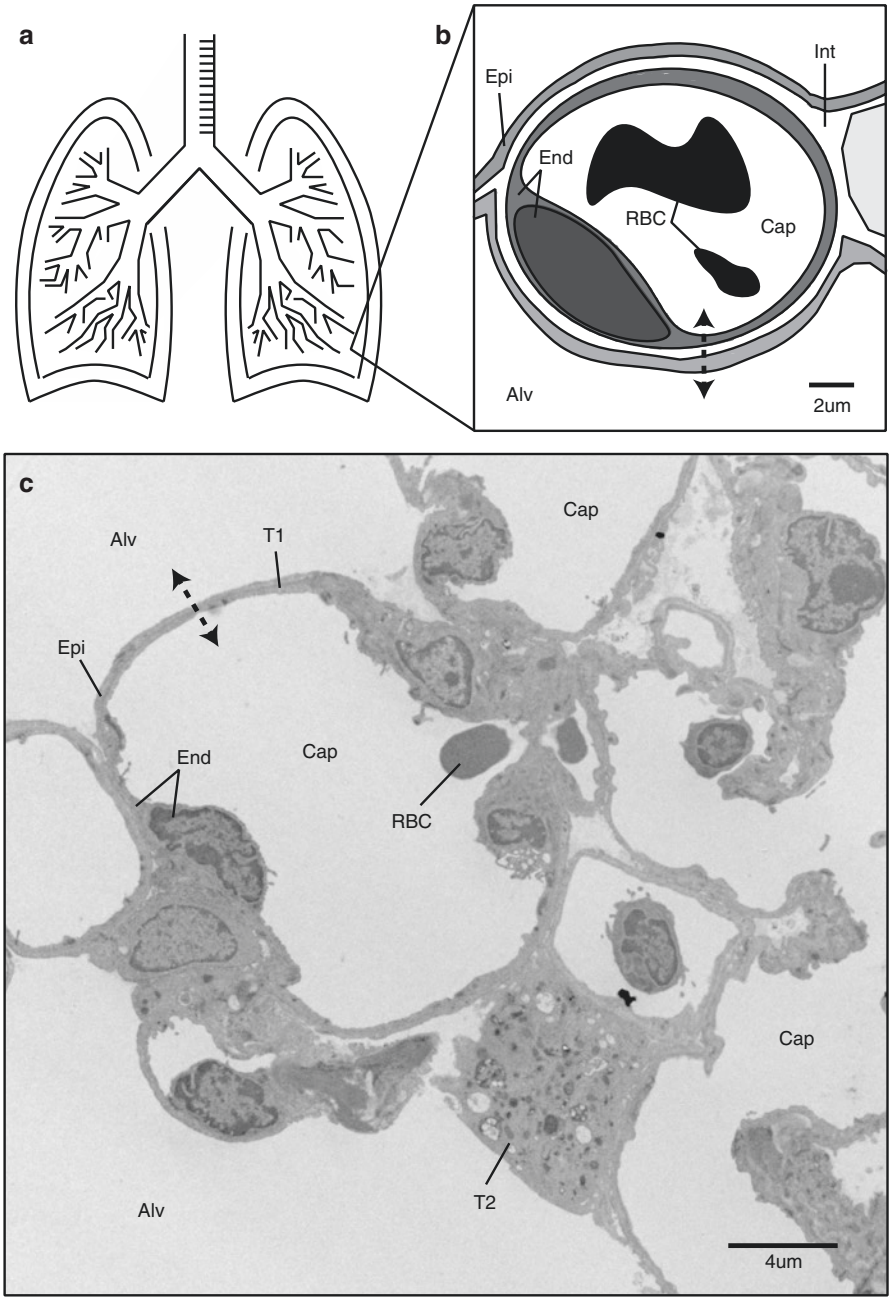

Fig. 1.1 (**a**) Gas exchange occurs at the distal airways, also known as the transitional and respiratory zones. Illustrated (**b**) and electron microgram (**c**) cross sections of pulmonary capillaries (Cap) embedded within alveoli (Alv). The double-sided arrow indicates the diffusion pathway of gases across the air-blood interface. This interface, also referred to as alveolo-capillary membrane, consists of alveolar epithelium (Epi) juxtaposed to capillary endothelium (End) through the respective basement membranes. Type I (T1) and type II (T2) pneumocytes can be visualized on the electron microgram

Once O_2 arrives in the alveoli, the primary force driving it into the blood is the partial pressure gradient across the alveolo-capillary membrane, which is the difference between P_AO_2 and the partial pressure of O_2 in returning mixed venous blood. As seen in the equation, P_AO_2 comprises of the difference between the partial pressure of inspired oxygen within the airway ($[(P_{atm} - P_{H_2O}) \times F_IO_2]$) and the drop in the partial pressure of O_2 due to diffusion of O_2 into the capillary blood (P_ACO_2/R). Apart from F_IO_2, the other variables are relatively fixed. By increasing F_IO_2, P_AO_2 is also increased, increasing the partial pressure gradient between alveolar O_2 and mixed venous O_2, increasing the driving force for O_2 diffusion from the alveoli into the blood.

Carbon dioxide is a natural byproduct of cellular metabolism and is carried by the venous system to the pulmonary capillary bed where it diffuses into the alveoli and is excreted into the atmosphere. Unlike oxygen delivery, the elimination of carbon dioxide is determined primarily by ventilation. The mean alveolar partial pressure of CO_2 is determined by the following equation where F_ACO_2 = fraction of alveolar CO_2, $\dot{V}CO_2$ = rate of CO_2 production by the tissues, $\dot{V}_E$ = minute ventilation, and $\dot{V}_d$ = dead space ventilation [1, 2].

$$F_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_E - \dot{V}_d}$$

The expression ($\dot{V}_E - \dot{V}_d$) represents alveolar ventilation rate, or the volume of inspired air that participates in gas exchange. In this equation, $\dot{V}CO_2$ is a function of metabolic processes and $\dot{V}_d$ is anatomically set whereas $\dot{V}_E$ is acutely modifiable. Minute ventilation is the product of tidal volume and respiratory rate. By modifying either of these variables, the amount of CO_2 eliminated can be increased or decreased. For example, if tidal volume or respiratory rate increases, F_ACO_2 decreases, increasing the partial pressure gradient between the mixed venous blood and the alveoli, driving more CO_2 into the alveoli.

As discussed, O_2 is delivered to the site of gas exchange by ventilation and removed by perfusion, whereas CO_2 is delivered by perfusion and removed by ventilation. For optimal gas exchange, ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) must match. The ideal $\dot{V}/\dot{Q}$ ratio is 1. This value is achieved in the middle portions of the lung in erect subjects. However, up the lung from the base to the apex, $\dot{V}/\dot{Q}$ ranges from 0.3 to 2.1 [3]. The value of $\dot{V}/\dot{Q}$ affects the value of P_AO_2 and P_ACO_2 and thus gas exchange (Fig. 1.2). If a region of lung is perfused but not aerated, for example because it is filled with edema fluid, $\dot{V}/\dot{Q}$ is zero and O_2 cannot enter nor CO_2 leave. As a result, the venous blood is shunted through the pulmonary circulation of that region, without participating in gas exchange and thus retains O_2 and CO_2 partial pressures of mixed venous blood. Physiologically, this shunting of deoxygenated, hypercarbic blood can severely decrease O_2 saturation and content in the arterial blood, causing an increase in the alveolo-arterial O_2 (A-a) gradient. The ensuing hypoxemia is refractory to an increase in FiO2. Shunting also reduces the efficiency of CO_2 excretion. If the subject is able to enact a compensatory rise in minute ventilation, shunting will not lead to hypercarbia. If instead minute ventilation is fixed, as is the case for example of a patient on controlled mechanical ventilation, shunting will lead also to CO_2 retention, in addition to hypoxemia. On the other hand, if a

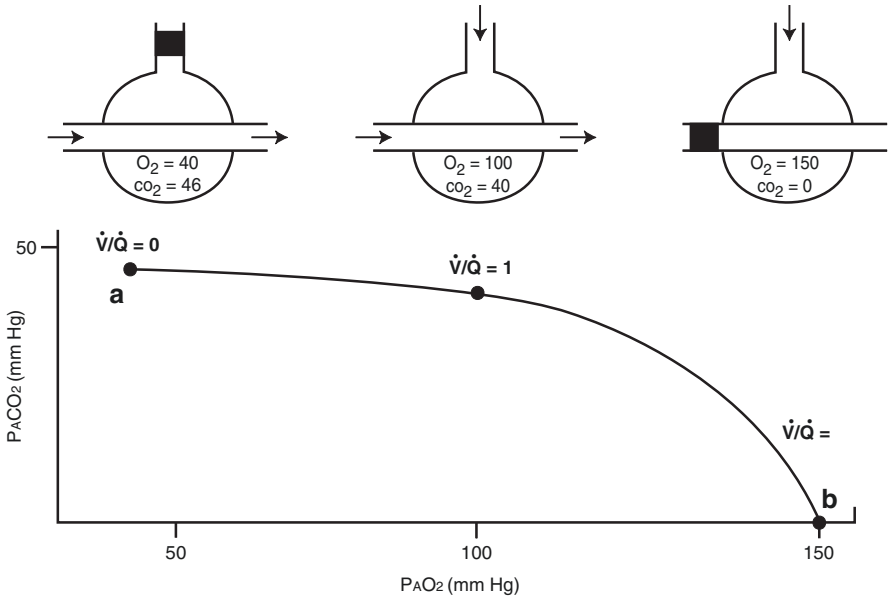

Fig. 1.2 O_2-CO_2 diagram illustrating the relationship between ventilation-perfusion ratio (V/Q) and alveolar oxygen (P_AO_2) and carbon dioxide (P_ACO_2) partial pressures in a lung unit. Lung units comprise of alveoli and pulmonary capillaries. Arrows denote airflow and blood flow. The curve represents the P_AO_2 and P_ACO_2 of all V/Q values between 0 and ∞. Point (a) illustrates shunting and point (b) illustrates dead space. (reproduced from reference [1] with permission)

region of lung is not perfused, for example because of a pulmonary embolus, but is ventilated, V/Q mathematically tends to infinity and such region functionally becomes dead space ventilation, with the partial pressures of both O_2 and CO_2 matching those of the conducting airways. Physiologically, extremely high V/Q alveoli increase alveolar dead space and dead space ventilation. The mismatch of V/Q can drastically affect the alveolar concentrations of both gases in different ways and have significant physiological effects on gas exchange.

The final component of gas exchange is diffusion of O_2 and CO_2 molecules between alveoli and pulmonary capillary blood. The gas molecules traverse the thin epithelial-endothelial membrane of the air-blood interface in opposite directions down their respective partial pressure gradients. The rate of gas movement (V) is primarily determined by Fick's law of diffusion where A = membrane surface area, ΔP = difference in gas partial pressure across the interface, and D = distance that the molecules must travel [1, 2].

$$\dot{V} = \frac{A(\Delta P)}{D}$$

Oxygen diffuses down a gradient from mean alveolar partial pressure (100 mmHg at room air) to a mixed venous partial pressure of 40 mmHg. Carbon dioxide diffuses from a mixed venous partial pressure of 46 mmHg to a mean alveolar partial pressure of 40 mmHg. The remaining parameters of Fick's equation are optimized

by the body to maximize diffusion. The air-blood interface is extremely thin (0.2–0.3 μm) with an enormous surface area of 70–80 m^2. These optimized conditions allow for rapid diffusion of gases even at higher blood flow. In fact, diffusing gases take only one-third of the 0.75-s pulmonary capillary transit time to equilibrate [2].

1.2 Respiratory Mechanics

Respiratory mechanics refers to lung function as described by relationships between pressure, gas flow, and volumes. Understanding it requires comprehension of the gross anatomy of the respiratory system. The respiratory system consists of the airway, lung, and chest wall. The chest wall comprises the rib cage and the diaphragm. Between the lungs and the chest wall is a virtual space, the intrapleural space. The pleural fluid in the intrapleural space serves two roles: lubrication of the adjacent, sliding pleural surfaces, and adhesion of the lung to the chest wall.

Within the respiratory system is the presence of opposing static forces, exhibited by the lung and chest wall which can be schematically viewed as two springs in parallel with one spring compressed below its resting volume (the chest wall) and one spring elongated above its resting volume (the lung) (Fig. 1.3) [4]. The lung naturally pulls inwards while the chest wall pulls outwards. With pleural fluid

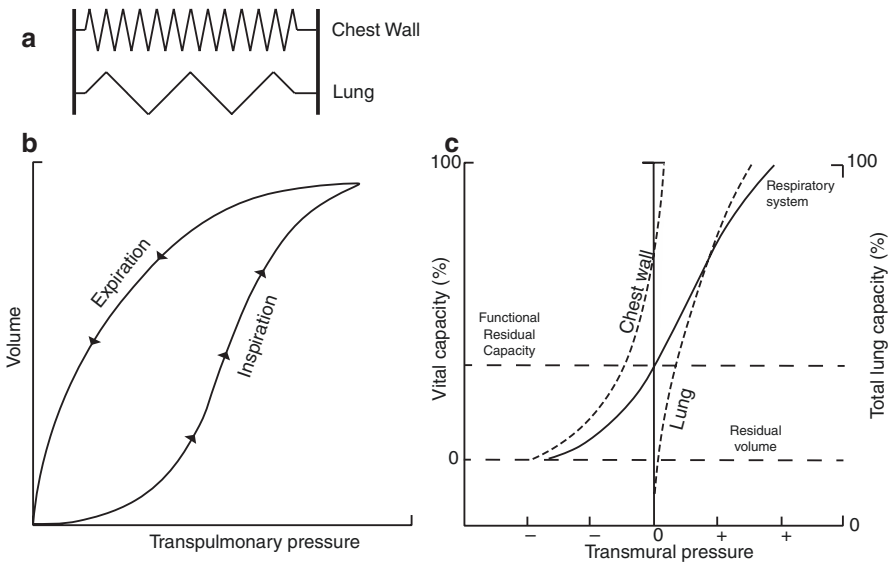

Fig. 1.3 (**a**) Parallel springs representing opposing static forces of the chest wall and lung. (**b**) Pressure-volume curve of air-filled lung during inspiration and expiration. (**c**) Pressure-volume curve of lung, chest wall, and respiratory system. The curve of the respiratory system is the sum of the lung and chest wall curves. The resting or equilibrium volume is the point where each curve intersects the *Y*-axis. The respiratory system is at equilibrium at the functional residual capacity (FRC). Panels (**b**) and (**c**) are reproduced from reference [1] with permission

adhering the two components, these opposing forces contribute to the structural integrity of the respiratory system and are essential for proper ventilation.

The lung's inward directed force results from two factors: the elastic recoil of lung tissue and surface tension. Elastic recoil refers to the tendency of an object to resume its natural shape after being stretched or compressed, and can be measured by its elastance (i.e., the pressure needed to provoke a unit volume change, $\Delta P/\Delta V$). The reciprocal of elastance is compliance, which refers to the property of an object to deform when subjected to an applied force, i.e., the change in volume per unit change in pressure ($\Delta V/\Delta P$). The compliance of the lung varies at different volumes. Lung tissue is generally more compliant and distensible at lower volumes and becomes stiffer and less compliant with increased volume [4]. This phenomenon can be appreciated by the pressure-volume curve of the air-filled lung on inspiration and expiration (Fig. 1.3). Notice the relatively steep slope of both curves at low to medium pressures and flattening of the curves near the upper limit of pressure values. The reduced compliance or increased elastic recoil at higher volumes is due to elastin and collagen fibers within the lung tissue. This increased elastic recoil at higher volumes is an intrinsic property of the lung and is one of the forces contributing to its inward pull.

The second factor that contributes to the inward pull of the lung is surface tension. Surface tension is the attractive force between adjacent liquid or air molecules. The surface of the alveoli is coated by a layer of fluid that is in contact with air, continuous with the airways, forming an air-liquid interface. Because the liquid molecules have greater attraction relative to the air molecules, they pack tighter together through cohesive forces which generate a collapsing pressure that tends to decrease the volume of the alveolus. The summation of these collapsing pressures across alveoli, as a result, pulls the lung inward [1].

A significant problem that surface tension poses is that it decreases the compliance of the lung especially at lower volumes, requiring increased effort to initiate inspiration. This phenomenon can be observed in the pressure-volume curve of the lung on inspiration (Fig. 1.3). Note the initial relatively flat part of the curve, which corresponds to reduced compliance. The lung must overcome surface tension to expand. To lessen this initial load, type II pneumocytes in the lower respiratory tract produce surfactant, a phospholipid that alleviates the restrictive effect of surface tension at low lung volumes, increasing lung compliance during initial inspiration without jeopardizing the lung's elastic recoil. Surfactant also acts as an alveolar "stabilizer" by maintaining alveolar collapsing pressure (P_c) within an optimal range [5]. It does this by regulating the surface tension (T) as defined by the law of Laplace for spheres where P_c = collapsing pressure, T = surface tension, and r = radius [1, 4].

$$P_c = \frac{2T}{r}$$

By Laplace's law, reducing the radius of an alveolus will increase the collapsing pressure. This will prompt further reduction of alveolar radius and hence trigger a

positive feed-forward mechanism that would eventually lead to alveolar collapse. In fact, alveoli across the lung have varying radii (0.1–0.25 mm). In the absence of surfactant, the smaller alveoli would tend to collapse, transferring the collapsed volume to adjacent alveoli, which would instead increase in size, reducing their P_c and thus tending to enlarge even more. In theory, this could dramatically skew the range of alveolar volumes throughout the lung. Surfactant prevents this by maintaining a surface tension that discourages both alveolar collapse and hyperexpansion. It does so because when alveoli shrink, the molecules of surfactant get packed more closely together, thus repelling each other and lowering T. When instead alveoli expand, the molecules of surfactant become more rarefied in the liquid lining of the alveoli. This reduces their tensioactive power, leading to an increase in T which opposes the expansion by restoring higher P_c. Consequently, the absence of surfactant can result in stiff, heterogeneously aerated lungs with atelectatic areas interspersed with hyperexpanded areas [6].

Contrasting the inward pull of the lung is the natural tendency of the chest wall to pull outward. Relative to the lung, the chest wall has a larger resting volume. The main factor responsible for this is the natural outward elastic recoil of the chest wall, mainly due to cartilage, bone, and muscle.

The inward pull of the lung and the outward pull of the chest wall adhered together by the pleural fluid create a dynamic relationship between opposing forces. The point where these opposing forces balance each other is the point where the system is in equilibrium. As the system deviates from equilibrium, it is pulled back into equilibrium by a corrective force. This is thus a typical case of stable equilibrium.

The equilibrium between the inward pull of the lungs and the outward pull of the chest wall is best illustrated through the pressure-volume curves of the relaxed lung, chest wall, and respiratory system (Fig. 1.3) [1]. The curves show the transmural pressure across each of the 3 structures at volumes ranging from residual volume (RV) to total lung capacity (TLC). The curve representing the lung shows that even at residual volume the transpulmonary pressure (i.e., alveolar pressure minus pleural pressure) is positive, indicating that the lungs maintain an inward elastic recoil. The chest wall curve instead shows that the transthoracic pressure remains negative (i.e., the pleural pressure is lower than atmospheric pressure) up to volumes that approach TLC. The curve representing the respiratory system is a summation of the curves representing the lung and the chest wall, and is generated by calculating the sum of the transpulmonary pressure and the transthoracic pressure at various volumes. The point where the respiratory system curve crosses the y-axis, demarked as the functional residual capacity (FRC), is the point whereby the system reaches its equilibrium volume and the inward recoil of the lung is balanced by the outward recoil of the chest wall. At higher volumes, there is positive intrapulmonary (i.e., alveolar) pressure which forms a gradient that pushes air out, moving the curve back to FRC. The opposite is true for volumes below FRC.

Ventilation occurs when the respiratory system expands above or deflates below, and then returns, to its resting or equilibrium volume. The cerebral cortex and the midbrain regulate inspiration via the medullary respiratory center's dorsal and

ventral respiratory groups (DRG/VRG). Inspiration is initiated by activation of the diaphragm and external intercostal muscles through the phrenic and intercostal nerves, respectively. The diaphragm contracts and depresses inferiorly while the external intercostals pull the ribs and sternum up and outwards, increasing thoracic cavity volume. The increase in thoracic volume decreases the intrapleural pressure and consequently the intrapulmonary (i.e., alveolar) pressure (Fig. 1.4). This causes a negative intrapulmonary pressure relative to the atmospheric pressure, producing a pressure gradient which promotes the inward movement of gas until the intrapulmonary pressure equalizes with the atmospheric pressure. Forced inspiration involves recruitment of additional muscles (i.e., sternocleidomastoid, scalene, and pectoralis minor) which cause a larger chest expansion and a larger pressure gradient, thus increasing the flow and volume of inward bound air [1].

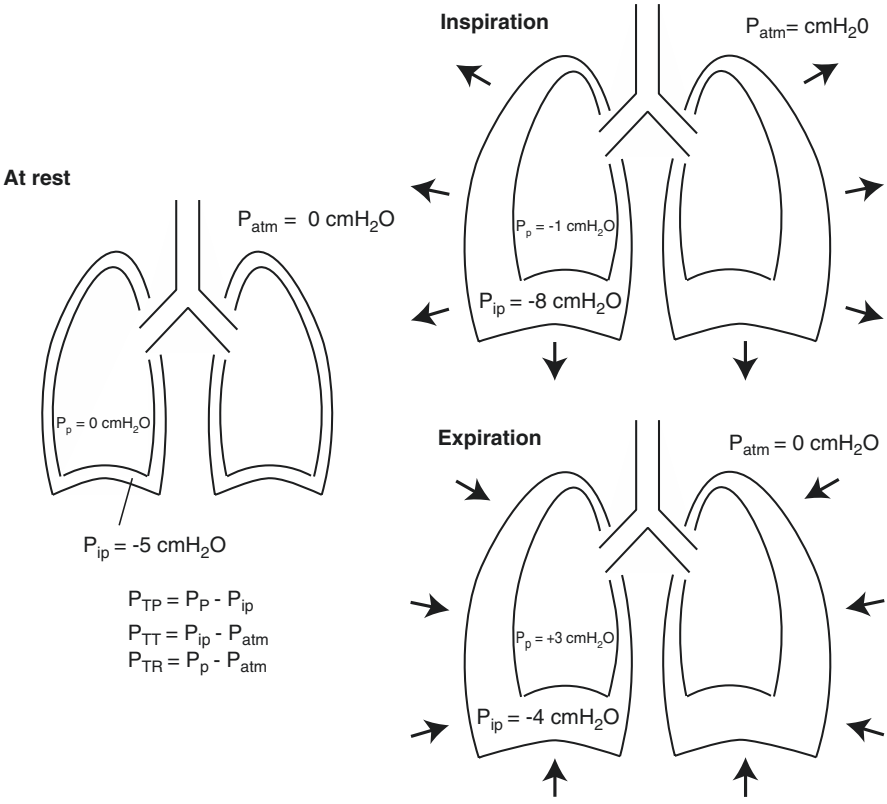

Fig. 1.4 Respiratory mechanics during inspiration and expiration. Contraction of the inspiratory muscles causes pressure changes that result in inward bound gas flow and hence increase in lung volume. When inspiration ceases, the elastic recoil of the respiratory system reverses the gradient between intrapulmonary and atmospheric pressure, resulting in expiratory airflow. P_p intrapulmonary pressure, P_{ip} intrapleural pressure, P_{atm} atmospheric barometric pressure, P_{TP} transpulmonary pressure, P_{TT} transthoracic pressure, P_{TR} transrespiratory pressure

Expiration is usually a passive process, requiring no muscle activity and solely based on the elastic recoil of the lung. At the end of inspiration, stretch receptors within the thoracic cavity inhibit the VRG, inhibiting further action potentials to the diaphragm and external intercostals. The respiratory system's elastic recoil then causes the intrapulmonary pressure to become positive relative to the pressure in the upper airways and atmosphere, creating a pressure gradient that promotes outward flow of air (Fig. 1.4). Forced expiration entails activation of the abdominal muscles (i.e., external/internal oblique, transverse abdominis, and rectus abdominis) and the internal intercostals, resulting in a larger increase in intrapulmonary pressure than by elastic recoil alone. This added force increases the flow of air and the expired volume [1].

Both inspiration and expiration involve the flow of gas through the airways. A first-approximation model to describe this process is Poiseuille's laminar flow model of either liquid or gas flowing through a tube [6]. This model is based on the equation below where Q = liquid or gas flow, ΔP = pressure gradient at the two ends of the tube, and R = resistance.

$$\dot{Q} = \frac{\Delta P}{R}$$

From this equation we can derive specific relationships, such as that greater pressure gradients generate greater flow for a given resistance or that greater resistance decreases flow. Resistance for laminar flow follows the equation below where η is viscosity, l is tube length, and r is the radius of the tube.

$$R = \frac{8nl}{\pi r^4}$$

Thus, the radius of a tube can significantly affect the resistance, and by extension the flow through a tube, because r appears in the above formula to the fourth power. The conducting airways (bronchi) have large diameters. The smaller bronchioles have tiny radii but their total cross-section is massive. Consequently, the major point of pressure drop along the bronchial tree is the medium-sized bronchi. At the respiratory bronchioles, gas flow stops, and diffusion is the predominant process driving respiratory gases across the alveolar membrane.

The factors that affect airway resistance follow the principles established by Poiseuille's law. The first factor is lung volume. Larger lung volumes decrease resistance while smaller lung volumes increase resistance. As the lung expands, the airways are dilated due to the radial traction of the surrounding lung tissue. At very low lung volumes, airways may close completely, especially in the lower part of the lung. The body also utilizes the autonomic nervous system to regulate airway diameter through smooth muscle tone. Sympathetic activity causes bronchodilation through β2 adrenergic receptors while parasympathetic activity causes bronchoconstriction through muscarinic receptors. Finally, the viscosity of the inhaled gas can affect the resistance, with higher viscosity causing higher resistance and lower flow rates [1].

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A Short History of Mechanical Ventilation

2

Philippe R. Bauer

2.1 Respiration, Circulation, and Their Interaction

The importance of the respiratory system was already invoked in the Bible as the breath of life: "And the Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life" (Genesis 2:7) [1]. The discoveries that led the mechanical ventilation span over two centuries (Fig. 2.1). The discovery of the respiratory system itself is attributed to Aelius Galenus or Galen, a Greek physician, in the second century AD, for his anatomical work entitled "*De usu partium corporis humani"* on the trachea and lungs in animals, the first reported mechanical insufflation of the lungs and the interaction between respiration and circulation. Leonardo da Vinci demonstrated that air enters the lungs through the bellows action of the chest wall. The first application of positive pressure ventilation by inserting a tube into the trachea of animals is attributed to Andreas Vesalius in 1543 in his anatomical work entitled "*De Humani Corporis Fabrica*" [2]. In 1667, Robert Hook reproduced Vesalius' experiment successfully [1]. The thought process was that air going into the lungs cools the heart and blood going into the arteries cools the body [1].

2.2 Oxygen, Combustion, Metabolism, Homeostasis

Although suspected since 200 BC in various experiments on air combustion—including those by Leonardo da Vinci—, oxygen was discovered in 1774 simultaneously by Carl Wilhelm Scheele and Joseph Priestley, and Antoine Lavoisier demonstrated that oxygen is essential to both combustion and respiration [1]. Two major observations contributed to their discovery. The blood coming from the lung

P. R. Bauer (✉)
Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: Bauer.Philippe@mayo.edu

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200 AD	Discovery of the respiratory system
1543	Concept of positive pressure ventilation
1670	Concept of negative pressure ventilation
1774	Discovery of oxygen
1865	Principle of homeostasis
1913	Discovery of the laryngoscope
1928	Negative pressure ventilation (iron lung) and poliomyelitis
1944	Intermittent positive pressure oxygen therapy and chest trauma
1952	Positive pressure ventilation and poliomyelitis
1963	Engström universal respirator
1967	Acute Respiratory Distress Syndrome
1970	Extracorporeal membrane oxygenation
1975	Optimum positive end-expiratory pressure
1987	Concept of baby lung
2000	Low tidal volume strategy
2015	Importance of driving pressure
2019	COVID-19 pandemic and strategic stockpile

Fig. 2.1 Timeline of the history of mechanical ventilation

is redder than the blood going into the lung indicating that "something" (that is oxygen) is brought into the blood when it passes through the lung. The fact that the temperature of the blood coming out of an organ is warmer led to the discovery of metabolism and carbon dioxide and water production as well as the concept of regulation of the internal environment or homeostasis by Claude Bernard in 1865.

2.3 The Dawn of Mechanical Ventilation

The first type of mechanical ventilators provided negative pressure ventilation using the Sauerbruch's method based on the differential pressure [3]. The concept of applying an external negative pressure ventilation was developed by John Mayow in 1670 and the first model was designed by John Dalziel in 1832. The first prototypes were built in 1876 and the first human use of a tank respirator or "iron lung" occurred in 1928 at the Boston Children's Hospital in the USA in a young child with poliomyelitis and respiratory failure (Fig. 2.2a). Iron lungs were widely used during the epidemics of poliomyelitis which disappeared with vaccination. A portable iron lung coined the "turtle shell" was well appreciated by the patients allowing them to be mobilized (Fig. 2.2b). Some patients remained on long-term mechanical ventilation: one patient remained on negative pressure ventilation for 16 years at the Mayo Clinic. I remember back in France taking care of patients with tracheostomy and on conventional positive pressure ventilator in the 1980s who had become part of the hospital.

When a gas exchange abnormality was also present, negative pressure ventilation appeared insufficient [4, 5]. The benefit of intermittent positive pressure oxygen therapy (IPPOT), precursor of intermittent positive pressure ventilation (IPPV)

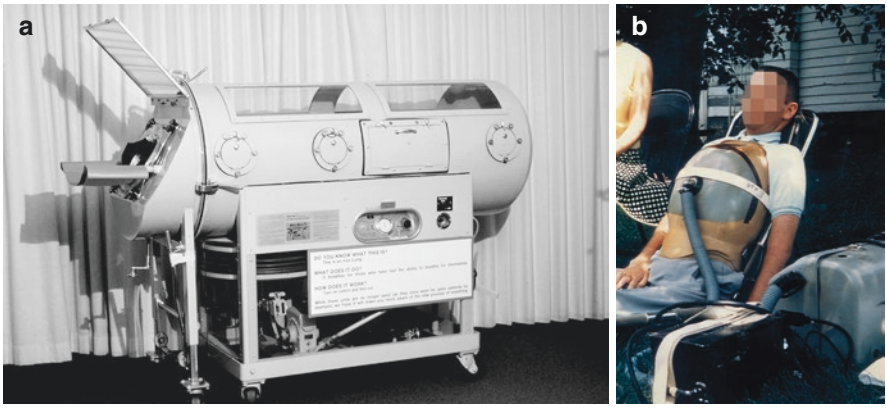


Fig. 2.2 (**a**) A negative pressure ventilator (iron lung) in display at the Mayo Clinic. (**b**) A portable iron lung (turtle shell) used by a Mayo Clinic patient

was discovered during the second world war to treat chest trauma that is the wet lung of trauma syndrome, also called posttraumatic respiratory insufficiency or respiratory distress syndrome [3], later coined acute respiratory distress syndrome (ARDS) by Ashbaugh in 1967 [4]. This led to the second type of mechanical ventilators which provided positive pressure ventilation. Their first use occurred during the 1952 poliomyelitis epidemic in Denmark, at the Blegdam Hospital in Copenhagen, in patients who underwent tracheostomy and positive pressure ventilation for "respiratory shock" [6]. The rapid decline in mortality associated with positive pressure ventilation led also to the rapid abandonment of the iron lungs. A flow sensitive breathing valve was developed by Bennett for high-altitude aviator oxygen delivery and applied to mechanical ventilation. In 1963, the Engström universal respirator was developed: a volume set, time-cycled with end-inspiratory pause [7]. First generation of positive pressure ventilators required electrical power. Aside explosion hazards, they were famous for their difficulty to adjust the acid-base status based on the actual tidal volume, sometimes unmasking a compensatory metabolic alkalosis in a setting of chronic respiratory acidosis. I remember vividly the challenge to prevent or correct alkalosis that could sometimes be severe. The development of blood gas analysis allowed prevention, detection and if necessary, correction of the acid-base status. The second generation of positive pressure ventilators were pneumatic device. The role of PEEP in preventing and correcting atelectasis was recognized [8] and sighs were often used as well as end-inspiratory pause. I remember that the Bennett MA-1 [9] had a PEEP limited around 17 cmH_2O and on the Siemens Servo Ventilator 900 series, the PEEP was easy to adjust on the lateral side of the machine but could be clogged by exhaled residues of nebulization. Other progresses included tracheal intubation, initially blindly by palpation of the neck and considered challenging. This led to the wider use of the laryngoscope discovered in 1913 independently by Chevalier Jackson and Henry Harrington Janeway and eventually the decrease of tracheostomy. In 1971, the introduction of an electronic feedback system with the SERVO provided a reliable way to set up a

ventilator. The latest generations of positive pressure mechanical ventilators are now equipped with microprocessor controls, various modes of ventilation and flow volume loop and other graphic displays. With time, emphasis has been made on ventilator synchrony like triggering, flow delivery, and adjustment to the respiratory drive, and include full ventilatory support like volume-controlled and pressure-controlled mandatory ventilation, airway pressure release ventilation, and partial ventilatory support like pressure support ventilation, proportional assist ventilation, neurally adjusted ventilatory assist and other proprietary modes of ventilation. Another technique, called high frequency oscillation, was short lived for its lack of efficacy. In the 1970s, Dr. Kolobow designed a successful membrane lung (known as the Kolobow lung) which was instrumental in the development of extracorporeal membrane oxygenation (ECMO) used when conventional mechanical ventilation has become insufficient to correct refractory cases of hypoxemic and hypercapnic respiratory acidosis [10].

Aside invasive modes of mechanical ventilation, noninvasive ventilation has also become popular with time. It was initially used in the 1940s for chronic conditions such as obesity-hypoventilation syndrome, obstructive sleep apnea, and neuromuscular diseases. Intermittent positive pressure breathing (IPPB), a pressure-cycled mode of noninvasive ventilation (IPPV), was popularized with the Bird Machine in 1955 and used in restrictive and chronic obstructive lung disease. It was short lived because of its brief duration of use but represents the precursor of pressure support ventilation [11]. Noninvasive ventilation has regained attention since the 1990s for acute conditions like chronic obstructive lung disease exacerbation, congestive heart failure exacerbation, and acute hypoxemic respiratory failure. It has become more attractive with the recognition of the potential deleterious effects of invasive mechanical ventilation. The interface was traditionally a mask or nasal pillows, but the use of a helmet has now gained popularity for its potential benefit in reducing intubation rates and mortality in patients with ARDS (Fig. 2.3).

2.4 Lessons Learned

The benefit of mechanical ventilation on reducing the work of breathing, providing adequate ventilation and oxygenation, is offset by the risk of ventilator-induced lung injury [2] that includes barotrauma with pneumomediastinum, pneumothorax and subcutaneous emphysema, biotrauma described as “the release of mediators by injurious ventilatory strategies, which can lead to lung and distal organ injury” [12] and more broadly speaking ventilator-associated complications. The deleterious effect of mechanical ventilation was already reported in 1944 by Macklin and Macklin who described the “malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions” [13]. The role of the PEEP, “helpful in combatting atelectasis and hypoxemia,” became prominent with the description of ARDS by Ashbaugh [4]. In 1975, Suter et al. proposed the “optimum end-expiratory airway pressure” or “best PEEP” “resulting in maximum oxygen transport (cardiac output times arterial oxygen content) and the lowest dead-space fraction [and] the greatest total static

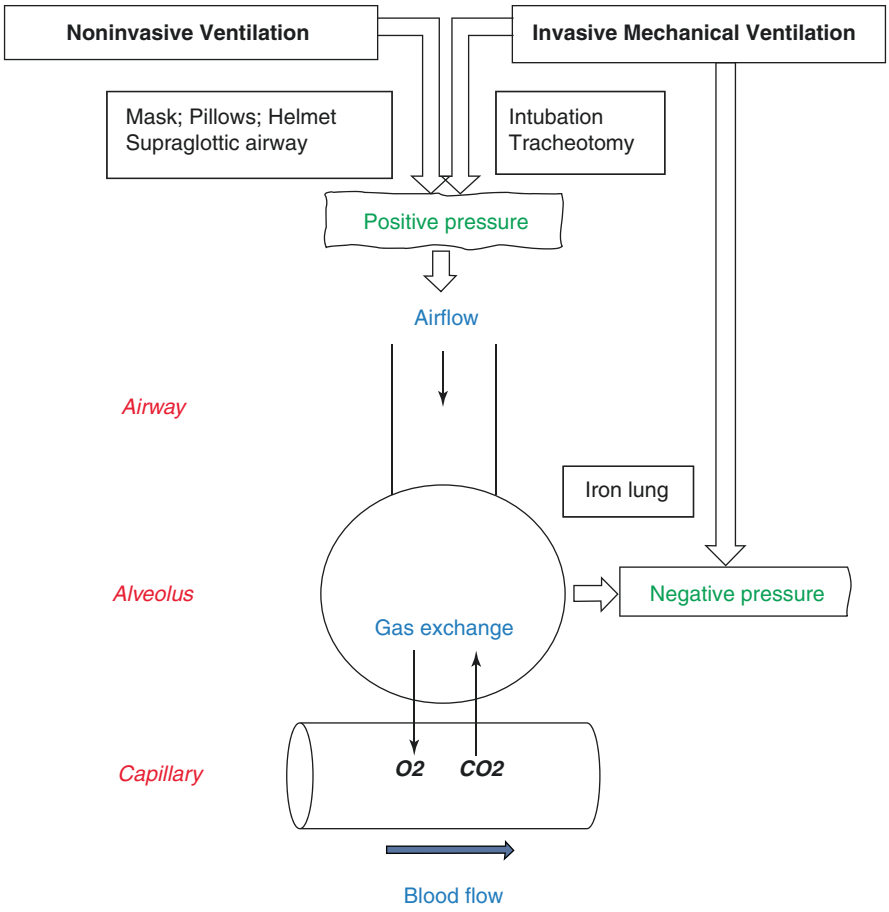


Fig. 2.3 The respiratory system coupled to the circulatory system and the different types of mechanical ventilation

compliance" [14]. There was also the need to prevent atelectasis associated with a low tidal volume and to minimize oxygen toxicity by limiting FIO_2. Ensued a time when patients were intubated and ventilated with high tidal volume (10 mL/kg of actual body weight), high PEEP, and often high peak and plateau pressure. I remember those times of frequent emergent chest tube placement and giant subcutaneous emphysema that came back in force with the current COVID-19 pandemic.

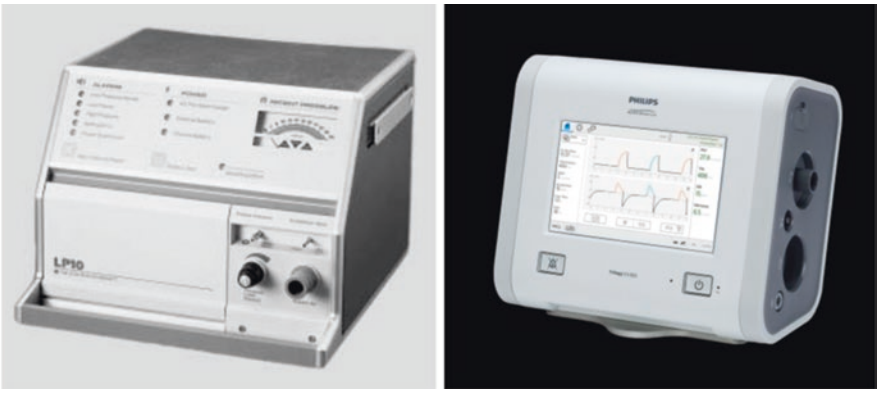
In the meantime, the concept of "baby lung" in ARDS was introduced by Gattinoni in 1987 from observation of the "non-homogeneous lung" in ARDS. Subsequently the concept of "shrinking baby lung" defined the progressive reduction in size and capacity for gas exchange in proportion to the severity of lung injury and emphasized the importance of avoiding the ventilator-associated lung injury vortex in acute respiratory failure by "following trends of gas exchange efficiency […], avoid labor breathing […], minimize oxygen demand and minute ventilation […], and prioritize low-stress tidal cycling" [15].

The benefits of minimizing tidal volume and plateau pressure were demonstrated by the landmark paper from the Acute Respiratory Distress Syndrome Network in 2000 that showed that an initial tidal volume of 6 mL/kg of predicted body weight and a plateau pressure of 30 cmH_2O of water or less resulted in decreased mortality when compared to a tidal volume of 12 mL/kg of and a plateau pressure of 50 cmH_2O or less [16]. While keeping a lower tidal volume and lower plateau pressure, the use of higher or lower PEEP resulted in similar outcome [17]. Further refinement in ventilator setting came with the concept of driving pressure, defined as tidal volume "intrinsically normalized to functional lung size" and measured as plateau pressure minus PEEP [18]. In 2015 in a landmark paper, Amato et al. showed that driving pressure change in relation to ventilator setting change was most associated with survival in ARDS and this should be considered when setting the ventilator [18]. These findings were confirmed by LUNG SAFE, a large observational study that showed that patients with a driving pressure of more than 14 cmH_2O on day 1 following intubation had a worse outcome [19].

The COVID-19 pandemic has demonstrated that the principles of lung protective strategy still apply. Intubation may be reduced using continuous positive airway pressure (CPAP). Neuromuscular blocking agents and prone positioning have been applied more frequently as well as rescue with extracorporeal membrane oxygenation. Yet, the proper titration of sedation remains a challenge. Finally, the timing of intubation (and extubation) should be judiciously decided to optimize the risk-benefit ratio of the invasive mechanical ventilation, while managing a de facto finite supply of ventilators or using a reserve inventory such as the US National Strategic National Stockpile Ventilators [20] (Fig. 2.4).

Examples of Ventilators Held by the Strategic National Stockpile in the United States

Covidien (Puritan Bennett) LP10 **Philips EV300**



https://www.aarc.org/resources/clinical-resources/strategic-national-stockpile-ventilator-training-program/

Fig. 2.4 Example of ventilators from the US National Stockpile during COVID-19 pandemic

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Airway Management in the Critically Ill

3

Sheila Nainan Myatra

3.1 Introduction

Tracheal intubation (TI) is one of the most commonly performed procedures in critically ill patients [1]. Critically ill patients have a *physiologically difficult* airway. The presence of physiological derangements such as hypoxaemia, hypotension, metabolic acidosis, neurological impairment, and right ventricular failure that may be present, increases the risk of complications during TI [2, 3]. Unlike in the operating room (OR), the often emergent nature of airway management, the critical illness, increased risk of aspiration, complex intubating conditions, limited access to advanced airway equipment and the presence of operators with varying level skills pose additional challenges during airway management in the ICU [4]. These are detailed in Table 3.1.

Several national studies and audits have shown high complication rates during TI in the critically ill. These complications include hypoxaemia, hypotension, arrhythmias, cardiac arrest and death [5–12]. The fourth UK National Audit Project report showed that major airway-related complications lead to death or brain injury in 61% of the cases in ICU, compared to 14% during anaesthesia [5]. Failure to use capnography, poor planning, poor recognition of high-risk airways, lack of advanced airway skills and equipment were major contributing factors. In the INTUBE Study, a large international prospective study on airway management in almost 3000 critically ill patients, at least one major adverse peri-intubation event was observed in 45.2% critically ill patients undergoing TI, with cardiovascular instability being the most prominent event, observed in 42.6% of patients. Severe hypoxaemia and cardiac arrest were observed in 9.3% and 3.1%, respectively. Patients experiencing major adverse events were at higher risk of ICU and at 28 days mortality after

S. N. Myatra (✉)
Department of Anesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

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Table 3.1 Challenges associated with tracheal intubation in the critically ill

The ICU environment	
Infrastructure Equipment Monitoring Personnel Timing	Poor access to patient's head end, lack of space around the patient Advanced airway equipment such as a flexible bronchoscope, videolaryngoscope, etc. may not be readily available Patient monitors are usually placed at the head end of the bed may not be visible Availability of trained personnel for emergent TI may be variable An emergent TI may be required at any time of the day or night
The patient	
Airway assessment Challenging anatomy Risk of aspiration Preoxygenation Physiologically difficult airway Patient cooperation Waking up the patient	May be difficult or impossible due to lack of time or poor patient cooperative Maxillofacial trauma, cervical spine injury, airway injuries, burns, etc. The patient may not be fasted or have gastroparesis associated with critical illness Insufficient time for preoxygenation, inefficient preoxygenation caused by ventilation perfusion mismatch. Lack of physiological reserves may lead to rapid oxygen desaturation allowing less safe apnoea time for TI Poor physiologic reserve due to critical illness. The presence of hypotension, hypoxaemia, etc. may increase the risk of complications during TI The patient may be uncooperative due to critical illness Unlike in the OR, postponing airway management is not possible, as the critical illness mandates a definitive airway
The airway operator	
Variability in airway training, experience and skills Human factors	The airway operator may have limited airway management training and skills. An inexperienced junior doctor may be performing TI alone. The patient, ICU or operator-related factors, alone or in combination may produce a stressful situation for the operator which may affect performance. Cognitive overload, fixation errors, tunnel vision and poor communication may lead to an increased chance of errors

TI tracheal intubation, *OR* operating room

adjustment for underlying disease severity [13]. TI in critically ill patients is therefore a high-risk procedure [3].

Recognizing the high risk of complications in this vulnerable group, various international societies have developed guidelines to manage TI in the critically ill, with a focus on strategies to enhance patient safety [14–16]. Recent reviews have highlighted important strategies to minimize complications in these patients [17–20]. This chapter will provide updated evidence optimizing first-pass success and maximizing patient safety during TI in critically ill patients. Tracheal extubation and tracheostomy will not be covered.

3.2 Indications for Tracheal Intubation in ICU

The most common indications include:

1. Facilitation of invasive mechanical ventilation (inadequate oxygenation/ventilation, avoidance of hypercarbia, controlled hyperventilation, need for neuromuscular paralysis, postoperative elective ventilation).

2. Protection of the respiratory tract from aspiration of gastric contents.
3. Haemodynamic instability—shock, cardiac arrest, etc.
4. Relief of upper airway obstruction.
5. Tracheobronchial toileting.

3.3 Planning and Preparation for Tracheal Intubation

3.3.1 Clinical History and General Examination

The often emergent nature of TI in the critically ill may leave little or no time for obtaining a good clinical history and examining the patients. However, every effort should be made to obtain relevant clinical history and examination findings prior to TI. In addition to clinical history related to the present illness and comorbidities, specific history related to airway management such as the time of last oral intake, contraindications to use succinylcholine or other drugs, drug allergies, presence of dentures, loose or missing teeth, history of sleep apnoea and a previous history of a difficult TI should be elicited from the patient or family. Examination of the cardiorespiratory system and other systems should be performed along with a review of relevant laboratory investigations and imaging reports.

3.3.2 Airway Assessment

A thorough airway assessment may not be feasible due to lack of time or the patient being uncooperative. In a systematic review and meta-analysis of over 30,000 patients in the OR, the upper lip bite test (the inability to bite the upper lip with the lower incisors), a short hyomental distance, retrognathia and the modified Mallampati were shown to have a positive likelihood ratio of 14, 6.4, 6 and 4.1 respectively to predict a difficult airway [21]. The 12-point MACOCHA (**M**allampati class, presence of obstructive sleep apnoea OS**A**, **C**ervical spine mobility, mouth **O**pening, presence of **C**oma or **H**ypoxia, and presence of an **A**nesthesiologist) score (Table 3.2) proposed for airway assessment in the critically ill patients takes anatomical, physiological and operator skills into consideration to predict a difficult airway [22]. It is simple to perform and may be more suitable for use in critically ill patients.

3.3.3 Airway Cart and Checklists

An airway cart with all of the necessary items to facilitate TI, rescue oxygenation and haemodynamic support should be available near the patient prior to TI [14, 16]. Checklists may be helpful to ensure that the essential items and preparations have been undertaken prior to TI and are recommended in guidelines [16]. However, a randomized trial investigating the use of a written checklist prior to

Table 3.2 MACOCHA Score [22]

Factors	Points
Factors related to patient	
Mallampati score III or IV	5
Obstructive sleep apnoea syndrome	2
Reduced mobility of cervical spine	1
Limited mouth opening	1
Factors related to pathology	
Coma	1
Severe hypoxaemia	1
Factors related to operator	
Non anesthesiologist	1
Total score	12

TI in ICU compared to usual care found no difference in lowest oxygen saturation and lowest systolic blood pressure soon after TI between the groups [23]. The checklist used in this study however did not include interventions aiming at optimizing physiology, such as non-invasive ventilation, fluid loading, early use of vasopressors, etc. which may explain why it did not influence the selected outcomes. In addition, the participating centres were experienced with the use of checklists for other ICU procedures; therefore the control group may have had a high penetrance of the checklist items [23]. Nevertheless, a pre-intubation checklist, including essential strategies for physiological optimization, may be effective in less experienced hands, as observed following the implementation of the Montpellier intubation bundle, aimed at reducing life-threatening complications associated with TI [24].

3.3.4 Team Preparation

Considering the complexities and high risk of TI in ICU, advance team preparation and planning is paramount. Having two airway operators for TI, with at least one being experienced has been shown to reduce complications [24]. There should be clear communication among the team members about the airway concerns, airway plan, the roles and responsibilities of each team member, the backup plan and the rescue plan before proceeding to performing TI.

3.4 The Tracheal Intubation Procedure

The physiological derangements present in critically ill patients increase the risk of complications during TI. Hence it is essential to optimize patient physiology and adopt strategies to improve first-pass TI success, to avoid complications. These strategies have been outlined in Table 3.3.

Table 3.3 Important considerations during tracheal intubation in the critically ill

Airway intervention	Important considerations
Airway assessment	Consider using the MACOCHA score [22]
Team preparation	Presence of two operators (at least one experienced in airway management) Clear communication among the team members about the airway concerns, airway plan, backup and rescue plan with roles and responsibilities of the team members defined in advance
Patient positioning	Upright or 'ramped' position. This improves preoxygenation by preventing reduction in the FRC and may reduce the risk of pulmonary aspiration of gastric contents
Preoxygenation and apnoeic oxygenation	HFNO use for preoxygenation reduces intubation-related complications as compared with bag valve mask in patients who are not severely hypoxemic NIV should be the method of choice for preoxygenation in severely hypoxic patients Apnoeic oxygenation and gentle mask ventilation may be used after optimal preoxygenation to prolong the time to desaturation between induction and laryngoscopy, especially in patients at high risk for desaturation
Rapid sequence intubation	Should be considered in all patients
Induction of anaesthesia	Prefer intravenous ketamine or etomidate unless contraindicated
Neuromuscular blockade	Use intravenous rocuronium or succinylcholine unless contraindicated
Haemodynamics	Use fluids or vasopressors in the peri-intubation period to maintain haemodynamics Early use of vasopressors may be considered
Device selection for tracheal intubation	Use of a stylet or bougie should be considered for the initial tracheal intubation A VL should be immediately available for use. A hyper-angulated VL along with a rigid stylet should be preferred over a traditional geometry VL if available, in an anticipated difficult airway
Confirmation of tracheal tube placement	A mandatory confirmation using waveform capnography
Rescue oxygenation	Limit attempts at tracheal intubation to two Use face mask ventilation or a SAD to restore oxygenation In a failed intubation, if rescue ventilation is successful using mask ventilation or a SAD, consider performing a surgical or percutaneous tracheostomy or intubation through the SAD by an airway expert using a flexible bronchoscope Perform an emergency cricothyroidotomy if one cannot intubate and cannot ventilate the patient. Alternately, a surgical tracheostomy may be considered if a surgeon experienced to perform it is immediately available
Action following a difficult airway management	Monitor the patient for complications Treat airway oedema and examine the airway if required Documentation and counselling of the family and patient if feasible Team debriefing

(continued)

Table 3.3 (continued)

Airway intervention	Important considerations
Human factor considerations	Use a shared mental model for communication Follow an algorithmic approach to tracheal intubation to reduce cognitive load and improve the recognition and management of failure Advance training in both technical and non-technical skills for airway management

FRC functional residual capacity, *HFNO* high flow nasal oxygen, *NIV* non-invasive ventilation, *VL* videolaryngoscope, *SAD* supraglottic airway device

3.4.1 Patient Positioning

Whether *sniffing* or the *semi upright (ramped)* position (keeping external auditory meatus levelled with the sternal notch) is superior to improve glottic visualization and make TI easier compared with a patient positioned completely flat is still controversial [25]. A multicentre trial showed ramped position was associated with increased difficulty in TI compared to sniffing position. However, the ramped positioning used may be suboptimal in this trial and therefore these results should be interpreted with caution [26]. A large retrospective study showed that a combination of ramped plus sniffing positions significantly reduced complication rates in critically ill patients [27]. A prospective observational study showed improved first-attempt TI success when ramping was compared to supine position in the emergency department [28]. Though randomized clinical trials are lacking, the upright position does improve preoxygenation, prevents reduction in the functional residual capacity and may reduce the risk of pulmonary aspiration, which is much helpful in this vulnerable group of patients. Recent guidelines have recommended a head-up position, especially in patients at a high risk of aspiration or desaturation [14, 15].

3.4.2 Preoxygenation and Apnoeic Oxygenation

Critically ill patients are at a high risk of desaturation during TI [2, 3]. Oxygen delivery can be achieved using a simple face mask, standard or high flow nasal oxygen (HFNO), non-invasive ventilation (NIV) mask, or a combination of these devices. Standard nasal oxygen or HFNO can be continued during attempts at TI (apnoeic oxygenation). In addition to oxygenation, HFNO generates positive end-expiratory pressure [29]. NIV improves oxygenation PEEP delivery and ventilation by augmenting minute ventilation with pressure-supported breaths and decreasing the right ventricular preload and the left ventricular afterload [30].

Various preoxygenation and apnoeic oxygenation strategies to increase the safe apnoea period (time interval before desaturation after inducing apnoea) have been compared. In the PROTRACH study, patients without pre-existing hypoxaemia ($PaO_2/FiO_2 \geq 200$ mmHg) were randomized to HFNO (from induction to TI) or to oxygen by face mask for preoxygenation. Though HFNO failed to increase the lowest oxygen saturation during TI, patients in the HFNO group experienced a lower

incidence of TI-related complications [31]. The application of nasal cannula at 15 L/min during attempts at TI compared to standard care did not increase the lowest oxygen saturation during TI attempts in a randomized open-label study in 150 adults in a medical ICU [32]. In the FLORALI 2 study, critically adult patients undergoing TI were randomized to NIV or HFNO (from induction to TI). There was no difference in the incidence of severe hypoxaemia. However, in the subgroup of patients with a $PaO_2/FiO_2 < 200$, a potential benefit for NIV was seen [33]. Jaber et al. in a proof of concept study showed that adding HFNO for apnoeic oxygenation to NIV for preoxygenation was more effective in reducing the severity of desaturation during TI, compared to NIV alone [34]. More studies are required to confirm these findings.

Based on the recent literature, NIV seems to be the preferred method of choice for preoxygenation, especially in severely hypoxic patients. HFNO use has shown lesser complications related to TI as compared to bag valve mask preoxygenation in patients who are not severely hypoxaemic.

3.4.3 Induction of Anaesthesia

Drugs used for induction of anaesthesia can increase the risk of both haemodynamic and respiratory complications. Critically ill patients usually have reduced requirements for anaesthesia [35]. Ketamine and etomidate should be preferred in critically ill patients due to their positive haemodynamic profile [36]. Reducing the patient's minute ventilation during induction may blunt the respiratory compensation for metabolic acidosis, worsening acidosis and shock. Loss of a respiratory compensation during TI may exacerbate hypoxaemia present during induction [37].

3.4.3.1 Propofol

Propofol blunts the airway reflexes providing superior conditions for TI, even without the use of muscle relaxants. However, it may not be suitable in critically ill patients who are in shock, hypovolemic, with cardiac comorbidities having limited physiologic reserve, as there can be a precipitous fall in blood pressure and even bradycardia following its use. Retrospective studies have shown propofol use to be safe when various strategies to mitigate hypotension including fluid loading and vasopressor agents have been tried [38, 39]. Though ketamine and etomidate have been recommended as the induction agent of choice for TI in critically ill patients in various airway guidelines [14, 16], the INTUBE study showed that propofol still represents the most commonly used (42%) induction agent [13].

3.4.3.2 Etomidate

There have been concerns about adrenal suppression with the use of etomidate. A Cochrane analysis and a meta-analyses included observational studies and, showed that a single dose of etomidate was not associated with an increased mortality of critically ill patients [40, 41]. Corticosteroid supplementation may be considered if etomidate is used in patients with septic shock [42].

3.4.3.3 Ketamine

Ketamine is popular as an induction agent of choice unless contraindicated in critically ill patients, as it preserves the haemodynamics. No difference in intubating conditions or serious adverse events was found in a trial of 655 critically ill patients randomized to either etomidate or ketamine during RSI. However, there was a higher incidence of adrenal insufficiency in the etomidate group [36]. A study comparing the two agents in adult trauma patients showed no difference in first-pass success rates, ICU-free days, ventilator-free days or mortality used for RSI [43].

3.4.4 Controversies in Rapid Sequence Intubation

Critically ill patients may have gastroparesis associated with critical illness or may not be fasted at the time of TI. Thus, conventionally, a rapid sequence intubation (RSI) which involves administration of rapid onset agents (induction agent and muscle relaxant), cricoid pressure and avoidance of ventilation between induction and TI (to limit gastric insufflation and therefore pulmonary aspiration) is practised.

3.4.4.1 Use of Neuromuscular Blockade or Spontaneous Ventilation

RSI in critically ill patients is associated with greater first-attempt success and fewer TI-related complications [44–46] and should be considered in all patients. The use of neuromuscular blocking agents has been shown to improve mask ventilation, abolish upper airway muscle tone including laryngospasm, improve intubating conditions and optimize chest wall compliance. However, inducing apnoea in critically ill patients may result in rapid desaturation (secondary to loss of functional residual capacity, high metabolic rate, physiological shunt and ventilation perfusion mismatch), highlighting the importance of peri-intubation oxygenation and rescue oxygenation. The fear of inability to mask ventilate after giving neuromuscular blockade has led to reluctance in using these agents. However, recent guidelines recommend the use of these agents even during a cannot intubate, cannot ventilate emergency [14, 16]. No difference between the two agents with respect to oxygen desaturation, or successful first-pass TI was seen in a study comparing succinylcholine to rocuronium in critically ill patients [47]. Sugammadex may be used as an option for rapid reversal of rocuronium in an emergency [48]. However, there is limited data regarding its safety in critically ill patients. Succinylcholine may precipitate life-threatening hyperkalaemia in at-risk patients and thus should be used with caution.

Awake TI using a videolaryngoscope (VL) or flexible bronchoscope has a high success and safety in the OR. However, this requires patient co-operation and clinician expertise and may not be feasible in critically ill patients who are often unstable and uncooperative for this procedure.

3.4.4.2 Use of Cricoid Pressure

The use of cricoid pressure remains controversial. The Cochrane review concluded that more evidence is required [49]. A recent double-blind, randomized study

showed non-inferiority of sham versus cricoid pressure in preventing aspiration in patients at a high risk for aspiration [50]. Clinicians often have difficulty in identifying the cricoid ring. In addition, these is evidence that cricoid pressure may worsen the laryngeal view preventing successful TI and even mask ventilation [51, 52]. Nevertheless, several society guidelines still recommend the use of cricoid pressure during RSI [14, 16].

3.4.4.3 Mask Ventilation During RSI

Critically ill patients are at a high risk for hypoxaemia due to avoidance of ventilation between administration of neuromuscular blockade and TI during RSI. In the PREVENT study, 401 critically ill patients were randomized to receive mask ventilation or no ventilation between induction and TI [53]. Patients receiving ventilation experienced a lower incidence of severe hypoxaemia (oxygen saturation < 80%) without increasing the rate of pulmonary aspiration. Though this study was not powered for pulmonary aspiration, it provides some reassurance for gentle mask ventilation to limit hypoxia during RSI, especially in high-risk patients.

3.4.5 Haemodynamic Support During Tracheal Intubation

In the INTUBE study, there was a 42.6% incidence of cardiovascular instability following TI in critically ill patients [13]. The use of induction agents for anaesthesia, loss of sympathetic drive, hypovolemia and positive pressure ventilation may contribute to this. Haemodynamic instability is an independent predictor of adverse outcomes including mortality [12, 13]. The combination of hypotension and desaturation makes cardiac arrest even more likely [12]. Fluid loading and vasopressors are commonly used to prevent and treat hypotension. Fluid loading prior to TI as part of an TI bundle has shown to reduce life-threatening complications [24]. However, a recent trial showed no benefit with a routine fluid bolus prior to TI, although patients were not stratified by risk [54]. The early use of vasopressors instead to fluid loading to prevent hypotension during TI needs to be investigated.

3.4.6 Device Selection for Tracheal Intubation

3.4.6.1 Use of a Videolaryngoscope

A meta-analysis comparing direct laryngoscopy (DL) with VL for emergency TI outside the operating room, showed higher first-pass TI success rates with VL and fewer oesophageal intubations in the subgroup of ICU patients, though no difference in success rates was seen overall. The use of VL was associated with more life-threatening complications including hypotension [55]. A recent meta-analysis comparing VL with DL included nine randomized controlled trials with over 2000 critically ill patients. The use of VL did not improve first-pass success rate, even when evaluating the studies according to experience of the operator [56]. Some

studies included in these meta-analyses have shown higher incidence of severe life-threatening complications with VL use. An explanation given for these findings is failure to abort TI attempts when there is a clear laryngeal view using VL, leading to prolonged apnoea time and complications. There was heterogeneity in the studies included and some were of low quality. Nevertheless, though recent evidence does not support the routine use of VL for TI in ICU, VL improves glottic visualization as compared to DL making it an important tool for difficult airway management in ICU [57]. A hyper-angulated VL along with a stylet should be preferred over a traditional geometry VL if available, in an anticipated difficult airway. Future trials will better define the role of VL in ICU. Such trials should use first-pass TI success without complications as a primary outcome, rather than first-pass TI success rate alone [57].

3.4.6.2 Use of a Bougie

A recent randomized trial compared the use of a bougie with a tracheal tube and a stylet for TI in the emergency department in patients with at least one difficult airway characteristic [58]. There was significantly higher first-attempt TI success in the bougie group. This was a single centre study with operators experienced with the use of a bougie. Hence the generalizability of these findings is uncertain. Nevertheless, it seems reasonable to suggest that a bougie may be used to facilitate the initial TI in those experienced with its use.

3.4.6.3 Use of a Stylet

A stylet is commonly used to rescue a difficult tracheal intubation. The effect of routine use of stylet on first-pass success in critically ill patients has never been studied. Jaber et al. in randomized multicentre trial in 999 patients in 32 ICUs in France, compared the effect of TI using a tracheal tube with or without a stylet when performing direct laryngoscopy on first-attempt intubation success in critically ill adults. First-attempt intubation success was significantly better in the tracheal tube with stylet group compared to the tracheal tube alone group. There was no difference in the incidence of complications between the two groups [59].

The results of these two trials provide a strong rationale for the routine use of bougies and stylets for TI in the critically ill [60].

3.4.7 Confirmation of Tracheal Tube Position

Waveform capnography should be used to confirm TI (5–6 consistent waveforms with no decline) [14, 16]. Failure to use capnography resulted in 17 deaths or brain damage in ICU in the NAP4 report [5]. Oesophageal intubations and accidental tube displacements accounted for 82% of events leading to death or brain damage. This report strongly recommends the use of capnography for confirmation of TI in all critically ill patients [5]. However, despite the NAP4 report showing a high

incidence of adverse events due to failure to use capnography during TI, the INTUBE study published 10 years after this report showed that capnography was utilized in only 25% of patients to confirm proper tracheal tube placement. In addition, the study showed that capnography was not used in 70% of the patients who had an oesophageal intubation [13]. This highlights the importance of increasing global awareness and availability of capnography for improving the safety of airway management.

3.5 Rescue Oxygenation

If oxygen desaturation occurs during attempts at TI, mask ventilation should be performed to optimize oxygenation. Optimize mask ventilation with a two handed technique, using an oropharyngeal airway. If mask ventilation is inadequate, insert a supraglottic airway (SGA) device [14–16]. These devices form a seal around the laryngeal inlet and are inserted blindly. A second-generation SGA device should be preferred as it facilitates gastric decompression and provides a better laryngeal seal [14, 16].

Rescue ventilation using a SGA is often lifesaving in the critically ill. This skill should be learnt by all clinicians managing the airway of critically ill patients [61]. Since it is not used for routine airway management in ICU, critical care specialists are usually unfamiliar or untrained to use these devices. The NAP4 report concluded that in patients who were rescued using an emergent surgical airway, a SGA was not inserted in half of the cases. Moreover, it was often successful when inserted after performing a surgical cricothyrotomy, indicating that a cricothyroidotomy could have been avoided [5].

Following SGA insertion, successful rescue ventilation and restoration of oxygen saturation, one of the following options should be considered: TI through the SGA under bronchoscopic guidance by an airway expert or a surgical or percutaneous tracheostomy should be performed, since critically ill patients need a definitive airway for prolonged ventilation [14].

If SGA insertion is unsuccessful and the best attempt at mask ventilation, using an optimal technique and neuromuscular blockade is also unsuccessful an emergency cricothyroidotomy should be immediately performed, even if the oxygen saturation is preserved [14–16].

The optimal method for performing a cricothyroidotomy is still debatable. A surgical or wide bore cannula cricothyroidotomy (commercially available kits) should be performed. Needle cricothyroidotomy requires the use of trans-tracheal jet ventilation, which is usually not available in ICU.

Following an unanticipated difficult TI, monitoring the patient for further complications in essential. Watch for and treat airway oedema. Further examination of the airway by a specialist may be required, especially when airway trauma has occurred. Documentation of the airway difficulty along with counselling of the patient if feasible, or the family is essential [14].

3.6 Care and Maintenance of the Tracheal Tube

Following TI mechanical ventilation should be initiated if required, with the use of appropriate sedation. The marking on the tracheal tube corresponding to the level of the incisor (or nose) should be documented. The tracheal tube position should ideally be checked and the marking noted during each nursing shift to check for tube migration. Perform an X-ray chest after TI to confirm tracheal tube and nasogastric tube position. Nasogastric tube feeding, if required, should only be started after this confirmation. Maintain tracheal tube patency by performing tracheal suction as required, using a closed suction system. The tracheal cuff pressure should be checked daily using a cuff pressure gauge and maintained between 20 and 30 cm of H_2O at all times, to reduce the risk of pressure necrosis, mucosal ischemia and aspiration.

3.7 Human Factors in Airway Management

Considering the complexities and challenges involved during airway management in the critically ill, human factor considerations become extremely relevant. *Human factors* refer to how individual, team, patient, environmental and institutional characteristics influence human behaviour which, in turn, can affect both the clinician's technical and nontechnical skills during the process of airway management. Cognitive overload, loss of situation awareness, fixations errors and poor decision-making are known to occur in such stressful situations [14, 16]. According to the NAP-4 report, human factors contributed to at least 40% of instances of adverse outcomes. Inadequate training and experience, non-adherence to guidelines and failure to plan for failure were identified among the factors contributing to adverse outcomes [5]. Advance communication among the team members about the airway plan and backup plan including assigning roles and responsibilities to the team members may help overcome some of these problems. The use of cognitive aids, in simulation and real life, may improve technical performance and team communication in crisis situations; however, further research is required in this area [62]. The Vortex Approach [63] is one such cognitive aid developed to support decision-making processes and aid clinicians during an airway crisis.

3.8 Future Research

Future research is required to determine optimum interventions at increasing first-pass and identify better strategies to mitigate the high incidence of complications during TI, especially the haemodynamic complications which are seen in high proportion. The interventions aimed at increasing first-pass TI success should be integrated with those aiming at optimizing physiology. Future trials will better define the role of VL in ICU, especially with respect to the ideal glottis view required for a successful VL-assisted TI and the appropriate use of airway adjuncts. These trials

should use a composite end point of first-pass TI success rate without complications as a primary outcome, rather than first-pass TI success rate alone. Gastric ultrasound may help identify patients at risk of pulmonary aspiration and should be studied further in critically ill patients.

3.9 Conclusion

Critically ill patients have a physiologically difficult airway. TI remains a high-risk procedure in this vulnerable group of patients with an increased risk of complications. Recognition of the various challenges during TI in these patients and the use of appropriate strategies to improve first-pass TI success, while maintaining patient safety are paramount. Further research will help us determine the best strategies to improve patient outcomes.

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Controlled Mechanical Ventilation: Modes and Monitoring

4

Eduardo L. V. Costa, Glauco M. Plens, and Caio C. A. Morais

Controlled mechanical ventilation (CMV) occurs when the ventilator controls, during the inspiratory phase, one variable from the equation of motion (Eq. 4.1): either flow ($\dot{V}$) or airway pressure (P_{aw}). The reason one can only control one variable (either $\dot{V}$ or P_{aw}) at a time is that all the others are given constants (R_{rs} and C_{rs} are intrinsic properties of the respiratory system), derived variables (volume is the integration of flow), or determined by an independent control system (inspiratory and expiratory muscle pressure).

$$P_{aw}(t) = V(t)/C_{rs} + R_{rs} \times \dot{V}(t) + \text{PEEP} - P_{mus}(t) \tag{4.1}$$

where $V(t)$ is the instantaneous volume above end-expiratory volume, PEEP is the end-expiratory pressure, and P_{mus} represents the pressure generated by inspiratory and expiratory muscles. During strictly controlled mechanical ventilation, P_{mus} is zero, and the breathing pattern is monotonous.

The choice of which variable to control gives rise to the classically known pressure-controlled and volume-controlled modes. The term volume-controlled could alternatively (and more properly) be called flow-controlled mode as flow is controlled to achieve the target volume, but the former term is more commonly used.

According to the choice of ventilation mode, the controlling system receives a different task in the form of a target function defined by the user-adjusted ventilator settings. In pressure-controlled modes, this function consists of a target airway pressure (including a linear ramp with adjustable slopes) towards the inspiratory pressure. This pressure is then maintained during the set inspiratory time after which the pressure should fall as fast as possible to the user-defined PEEP level (Fig. 4.1a). To

E. L. V. Costa (✉) · G. M. Plens
Disciplina de Pneumologia, Universidade de São Paulo, São Paulo, Brazil

C. C. A. Morais
Division of Anesthesia, Critical Care and Pain Medicine, University of Harvard, Boston, MA, USA

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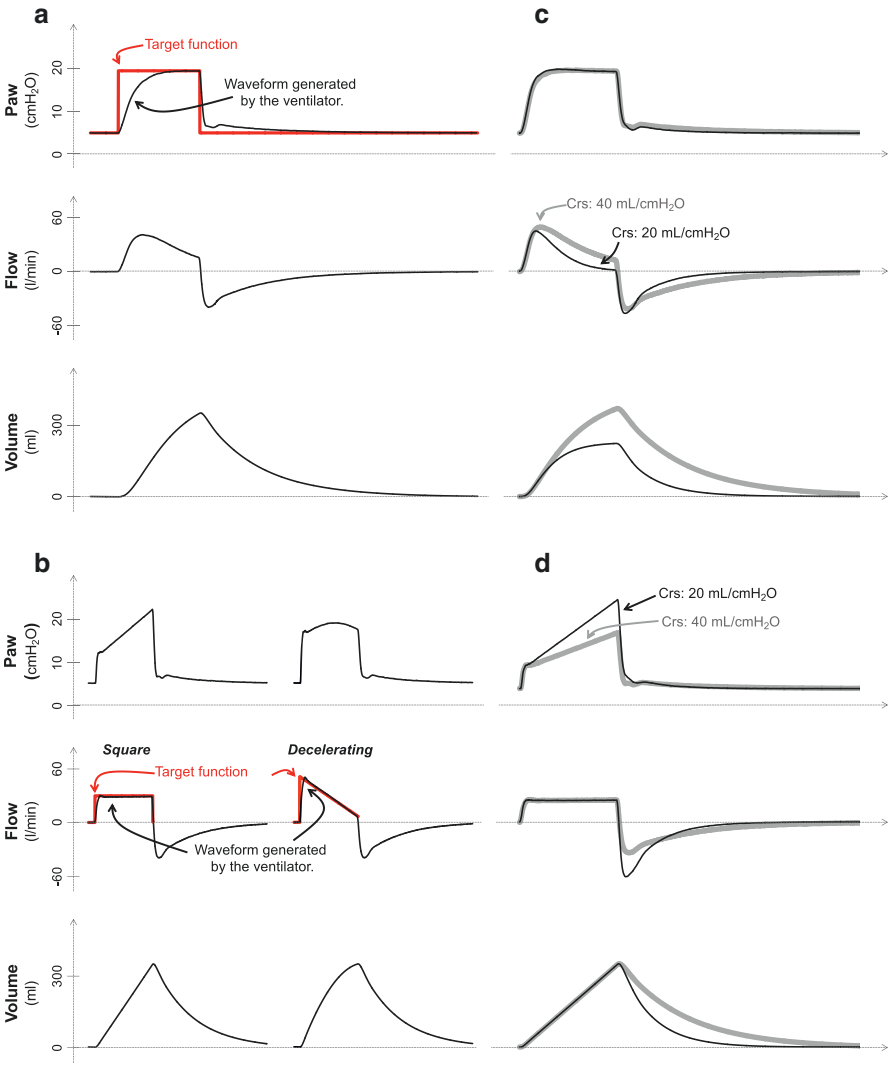

Fig. 4.1 Airway pressure (P_{aw}), flow and volume waveforms behavior during pressure-controlled ventilation (PCV, *panel* **a**), and volume-controlled ventilation (VCV, *panel* **b**). The line in red represents the target function in each mode. (**c**) and (**d**) illustrate the effect of changes in respiratory system compliance (C_{rs}) during pressure-controlled and volume-controlled modes, respectively. In PCV (**c**), the worsened C_{rs} reduces the delivered tidal volume. In contrast, in VCV (**d**), tidal volume is similar despite changes in C_{rs}; however, P_{aw} changes inversely to changes in C_{rs}

accomplish this task, the ventilator continuously receives inputs from pressure transducers and usually uses a "PID" controller, which defines the inspiratory flow generated by the inspiratory valve according to three estimates of distance from the target pressure: (1) flow is Proportional to the absolute difference in airway pressure from the set airway pressure, (2) flow increases when this absolute distance persists

over time (Integral), and (3) flow also depends on the error rate (Derivative). This is the basis of the statement that flow is free in pressure-controlled modes.

In volume-controlled modes, the PID control is more straightforward because control and target variables are the same. The target function is the flow in a predefined shape during inspiration. This way, the controller will determine how much electrical current to send to the proportional flow valves to reach the target flow waveform (Fig. 4.1b). Similar to pressure-controlled modes, the target function is the PEEP itself during expiration.

Although there is no evidence of a better choice of controlled ventilation mode in terms of outcome [1, 2], this decision certainly carries a handful of implications at the bedside, which we will explore in detail in this chapter.

4.1 Pressure-Controlled Ventilation

The mainstay of a pressure-controlled ventilation (PCV) is the application of a predefined pressure waveform (most commonly squared or trapezoid) at the airway opening (Fig. 4.1a). This implies that maximum airway pressures are set by the clinicians, a characteristic that can be particularly interesting when limiting pressures is considered a priority for lung protection and for avoidance of hemodynamic instability. For example, during PCV, it is possible to limit plateau and driving pressures irrespective of changes in respiratory system mechanics (Fig. 4.1), although these will affect the delivered tidal volume. Aside from external PEEP and fraction of inspired oxygen (settings common to all modes), only three parameters are set to define the target function: inspiratory pressure (maximum or increment above external PEEP), inspiratory time, either absolute or fractional (T_I/T_{TOT}), and mandatory frequency.

By choosing to control the pressure pattern, one must give up control over the flow and be aware of the necessity to closely monitor tidal volume and minute ventilation (Fig. 4.1c), which will inevitably vary according to the impedance of the respiratory system.

4.2 Volume-Controlled Ventilation

This ventilatory mode consists of ventilation with inspiratory airway flows in predefined, user-selected flow waveforms, the most common of which is square (Fig. 4.1b). In this case, airway pressure will vary according to respiratory mechanics (Fig. 4.1d). In several surveys, volume-controlled ventilation (VCV) was the most used ventilatory mode in critical care, although lately pressure-controlled and pressure-support modes have been increasingly more adopted. The main characteristic of VCV is the delivery of fixed tidal volumes, defined by the clinician. Because respiratory rate is also set, minute ventilation is guaranteed.

Apart from external PEEP, the target function is defined by the following settings: tidal volume, inspiratory flow, shape of flow waveform (squared, on some ventilators also sinusoidal or decelerating), and mandatory respiratory rate.

4.3 Pressure-Regulated Volume-Guaranteed Ventilation

Pressure-regulated volume-guaranteed ventilation (PRVG) is a closed-loop mode that offers the possibility of constant tidal volume in a pressure-controlled mode. Measured tidal volume serves as a feedback control variable for breath-by-breath automatic adjustment of pressure control. This ventilatory mode has various names, according to the manufacturer, such as pressure-regulated volume control (PRVC), AutoFlow, adaptive pressure ventilation, and others. Briefly, in the first cycle, the ventilator calculates respiratory system compliance during a VCV cycle. During subsequent breaths, the ventilator delivers the inspiratory pressure necessary to achieve the preset tidal volume based on the compliance calculation. This feature of PRVG is useful to account for ongoing changes in respiratory mechanics. On some ventilators, a high-pressure limit can be set to avoid injurious peak alveolar pressures in patients with low compliance. In the presence of spontaneous effort, tidal volume may increase or decrease frequently, causing the ventilator to often change pressure support, affecting patient comfort and work of breathing.

4.4 Physiological Features of Fully Controlled Modes

4.4.1 Lung Protection

In the absence of patient effort, PCV and VCV are comparable in terms of lung protection. Both modes can be set to avoid high values of driving pressures, plateau pressures, tidal volumes, and respiratory rates. In terms of limiting pressures, the settings in PCV can be more straightforward, but tidal volume requires close monitoring including careful settings of ventilator alarms (Fig. 4.1c). Conversely, in VCV, it is important to routinely measure plateau pressures and carefully set pressure alarms (detailed in the monitoring session; Fig. 4.3). A decrease in C_{rs}, for example, due to atelectasis or mucus plug, can result in higher airway pressures for a given tidal volume (Fig. 4.1d).

There is one important difference between modes in terms of peak airway pressure. Because of the decelerating flow waveform, typical of PCV, peak airway pressures are usually lower as compared with VCV with square-flow waveforms even for the same values of inspiratory time and tidal volume (Fig. 4.1a, b). The mechanism underlying this characteristic is that airway flows peak at the beginning of inspiration in PCV, when the lungs are only starting to inflate. Consequently, resistive pressure (P_{res}) decreases as elastic pressure (P_{el}) rises in contrast with square-wave volume-controlled modes characterized by constant P_{res} and increasing P_{el}. This lower peak airway pressure can be important especially when air leak is a

concern (e.g., laryngeal mask ventilation) [3]. However, it is important to stress that a given tidal volume will lead to the same plateau pressure both in VCV and PCV.

4.4.2 Alveolar Ventilation

After a step change in P_{aw}, either after triggering or after cycling-off, it takes a while before the alveolar pressure reaches equilibrium. It is possible to estimate the time needed to completely inflate or deflate the lungs using the concept of time constant. Briefly, considering that the respiratory system is adequately represented by one elastic compartment and one resistive element, which together produce monoexponential decays, the time constant can be defined as the product of R_{rs} and C_{rs}. After three to four times constants, near complete (95–99%) lung filling or emptying will take place.

This notion is essential for two main reasons involving the use of high respiratory rates. First, it is unusual to obtain complete lung filling at high respiratory rates. In PCV, inspiratory pressures sometimes much higher than alveolar pressures are required to generate enough inspiratory flow to allow for the delivery of tidal volume with a short inspiratory time. Even when accomplished, this goal comes with the risk of delivering too high tidal volume if, for example, airway resistance decreases suddenly, such as after bronchodilators. Correctly setting tidal volume alarms is imperative in this scenario. In VCV, by directly controlling tidal volumes, it can be easier to safely guarantee a short inspiratory time by applying short inspiratory pauses to monitor plateau pressures.

The second reason is to adequately set the ventilator to avoid the occurrence of intrinsic PEEP (detailed in the monitoring session; Fig. 4.3). When expiratory time is too short (less than three time constants), incomplete lung emptying will occur leading to intrinsic PEEP. For example, with a respiratory compliance of 40 mL/cmH_2O and airway resistance of 20 $cmH_2O\ L^{-1}\ s^{-1}$, the time constant will be 0.8 s, which means that the target expiratory time will be above 2.4 s. Here lies an important difference between PCV and VCV. If intrinsic PEEP occurs during VCV, tidal volume will not be affected, since it is controlled by the ventilator, but plateau pressure will rise. During PCV, plateau pressures will still be limited, but tidal volume will decrease. Of note, concerns regarding auto-PEEP or intrinsic PEEP should be minimal when minute volume is low, especially when below 10 L/min [4].

4.5 Modes Particularities During Inspiratory Effort

Presence of inspiratory effort changes mechanical ventilation substantially, since an independent control system (the respiratory center in the medulla) will now add muscle pressure (P_{mus}) to the equation of motion. How the ventilator responds to inspiratory effort is an important difference between pressure and volume-controlled modes, especially regarding delivery of inspiratory flow and changes in transpulmonary pressure.

Matching Inspiratory Flow Demand During VCV, inspiratory flow is preset by the healthcare provider. Matching flow demand from the patient can thus be difficult, especially while ventilating patients with high inspiratory drive. Low peak inspiratory flow can increase work of breathing and promote patient-ventilator dyssynchrony ("air hunger") (Fig. 4.2a).

Conversely, in PCV, the ventilator can respond more freely to different patient efforts (Fig. 4.2b). Patient comfort and synchrony with the ventilator can thus be more easily achieved [5]. If in VCV peak inspiratory flow is carefully adjusted to match patient demand, then this difference between PCV and VCV can be overcome, with little or no difference regarding work of breathing [2].

Transpulmonary Pressure Transpulmonary pressure is expressed as the sum of positive pressure applied by the ventilator and the absolute pressure generated by inspiratory muscles (P_{mus}). The presence of inspiratory muscle pressure will impact differently the transpulmonary pressure in PCV vs. VCV.

In PCV, negative pleural pressure swings promoted by the diaphragm signals the ventilator to increase inspiratory flow and tidal volume to match the patients' demand and keep airway pressure close to the set value (Fig. 4.2b). Transalveolar pressure, in this context, can be higher than the inspiratory pressure set by the clinician, since P_{mus} (unmeasured) will be added to the pressure generated by the ventilator, possibly leading to lung injury [6, 7].

Conversely, one possible advantage of VCV is to maintain constant transpulmonary pressure during inspiratory effort. Because flow is predetermined by the clinician, in the presence of patient effort, airway pressure will decrease, maintaining the preset tidal volume (Fig. 4.2a). This characteristic does not guarantee, however, that there will be no regional increase in transpulmonary pressure. This regional overdistension was demonstrated as intratidal movement of air between different lung regions leading to persistence of injurious patterns of inflation (e.g., pendelluft and tidal recruitment) during VCV [8].

Breath Stacking Another important difference between PCV and VCV is revealed when the inspiratory effort is longer than the set inspiratory time. A prolonged inspiratory effort may produce a consecutive ventilatory cycle, defined as double triggering asynchrony. In VCV, double triggering can induce an injurious "stacked" volume, which can be as much as twice the size of the set tidal volume if the respiratory cycles are separated by a short expiratory time. PCV mode can minimize the chance of excessive breath stacking because the delivered inspiratory flow depends on the pressure gradient between the airway and alveoli (Fig. 4.2).

4.6 Monitoring During Controlled Ventilation

Monitoring the mechanical properties of the respiratory system during passive ventilation is helpful to understand the pathophysiology of respiratory failure, set the mechanical ventilator, and minimize ventilator-induced lung injury. There are many

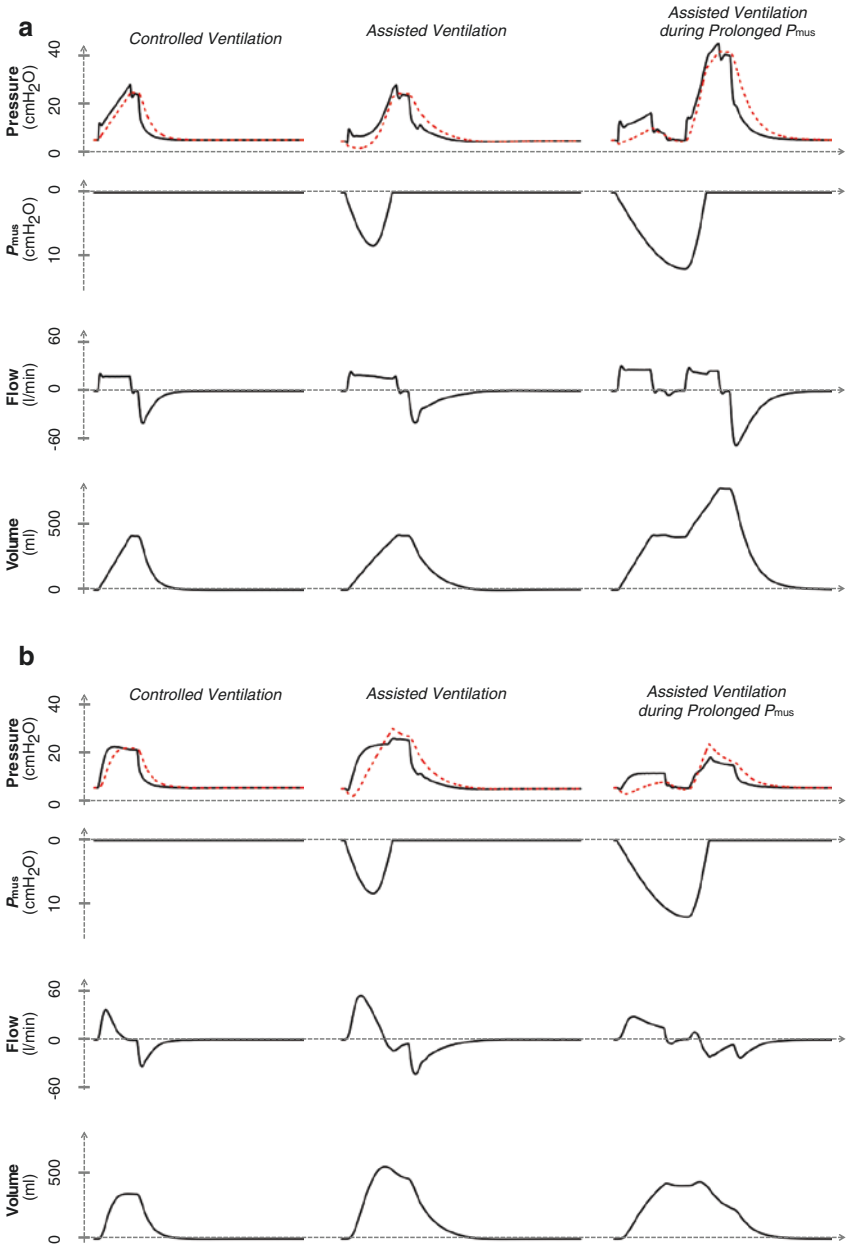

Fig. 4.2 Airway pressure, alveolar pressure (red dashed lines), muscular pressure (P_{mus}), flow and volume waveforms during controlled/assisted volume-controlled ventilation (VCV, *panel* **a**), and pressure-controlled ventilation (PCV, *panel* **b**). Note that in VCV, airway pressure decreases during assisted ventilation, with fixed inspiratory flow and volume. The limited flow can be associated with respiratory discomfort and is defined as "air hunger", which increases the risk of double triggering. In contrast, the assisted-PCV is associated with increased inspiratory flow, combined with higher alveolar pressure as compared to fully controlled ventilation. A P_{mus} longer than the set inspiratory time may produce double triggering asynchrony (right plot on *panels* **a** and **b**). Note the difference of "stacked" volume between VCV and PCV for a fixed P_{mus}; the true tidal volume delivered was calculated by integrating the flow-time waveform during the consecutive inspiratory cycles

methods to assess respiratory mechanics in static *(occlusion techniques)*, quasi-static (*low-flow pressure-volume (P–V) curves*), and dynamic conditions *(stress index)*. We refer to other chapters for advanced monitoring systems, such as esophageal manometry and electrical impedance tomography.

4.6.1 Static Measurements of Inspiratory Resistance and Respiratory Compliance

As previously presented, the equation of motion characterizes the mechanical forces required to overcome P_{res} and P_{el} of the respiratory system (Eq. 4.1). The inspiratory P_{res} will remain approximately constant applying a constant flow rate during VCV (Fig. 4.3a). An end-inspiratory occlusion (EIO) maneuver is required to interrupt flow and hold the lung volume at the end of inspiration. The EIO results in a rapid decay in the P_{aw}, from peak inspiratory pressure (PIP) to P_1, representing the pressure dissipated by the flow-dependent resistance (Fig. 4.3a). The rapid drop in P_{aw} can be followed by a slow decay until a plateau is reached (P_{plat}). The magnitude of the second decay depends on the viscoelasticity of the system (Fig. 4.3a). Thus, *inspiratory* R_{rs} can be obtained:

$$R_{rs} = \left(PIP - P_{plat}\right) / \dot{V}i \tag{4.2}$$

The average R_{rs} in healthy adults under controlled ventilation is ~10 $cmH_2O\ L^{-1}\ s^{-1}$. Changes in R_{rs} may occur during ventilation due to bronchospasm, reduced lung volume, and mucus production, leading to increased airway pressure (if a patient is under VCV) or reduced V_T (if a patient is under PCV).

The C_{rs} typically denotes compliance calculated from two pressure points during quasi-static conditions. An EIO allows the identification of P_{plat}, the alveolar pressure at end-inspiration, which represents the elastic end-inspiratory recoil pressure of the respiratory system. An end-expiratory occlusion (EEO) assesses the end-expiratory alveolar pressure ($PEEP_{tot}$) (Fig. 4.3a). Then, C_{rs} can be calculated as:

$$C_{rs} = V_T / \left(P_{plat} - PEEP_{tot}\right) \tag{4.3}$$

Prolonged EIO (>2 s) may cause underestimation of P_{plat} due to the viscoelastic properties and imperceptible leaks in the circuit. Thus, a shorter EIO (≤0.5 s) is recommended [9].

The measurement of C_{rs} during PCV is also allowed by many ventilators through an EIO (Fig. 4.3b). In the absence of an EIO, the inspiratory pressure will be close to P_{plat} during PCV only if flow approaches zero at the end of inspiration during PCV.

4.6.2 Low-Flow Pressure-Volume (*P–V*) Curves

The early use of *P–V* curves was performed by connecting supersyringes to the endotracheal tube, with complexity due to apparatus and the risk of lung collapse

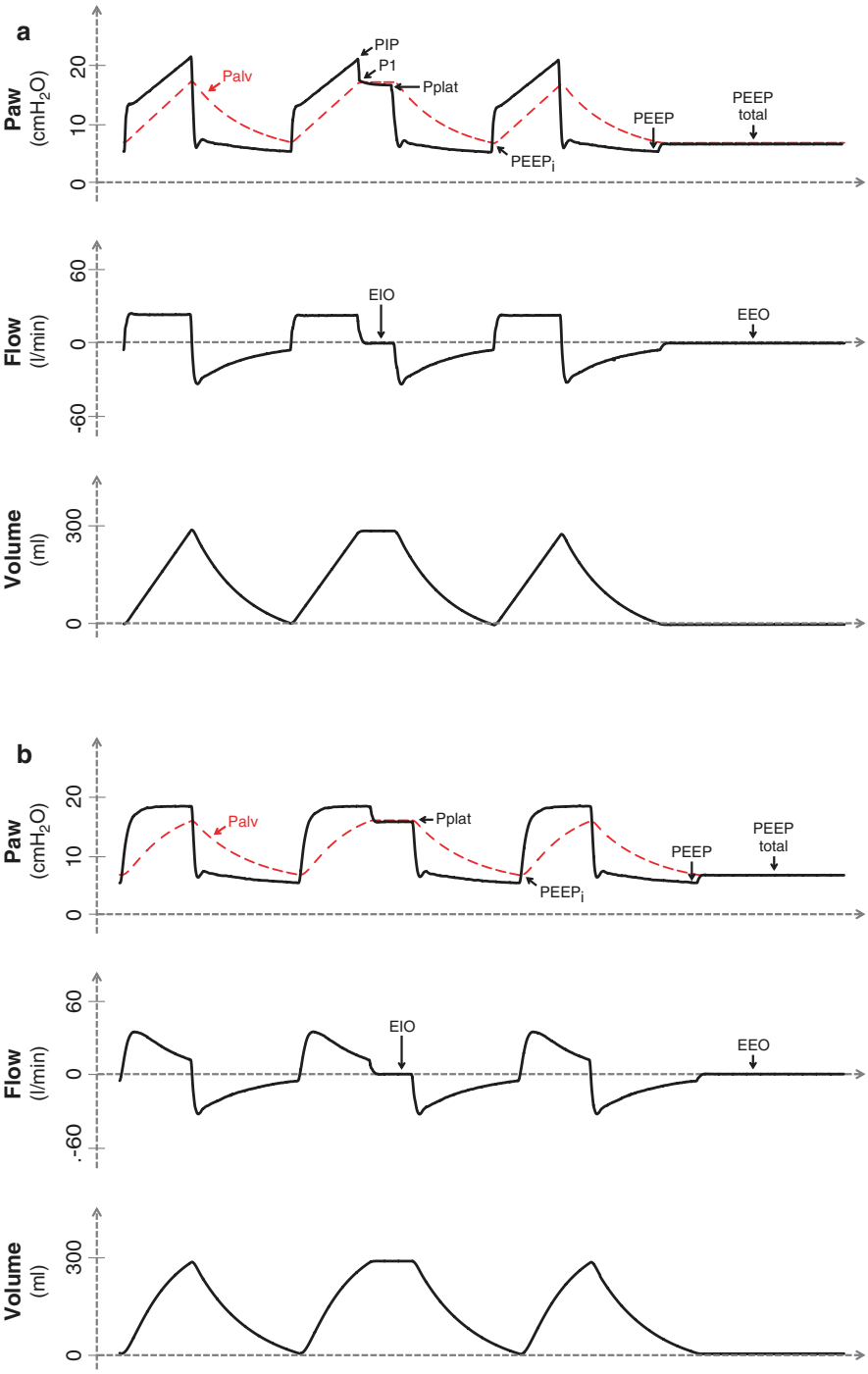

Fig. 4.3 Measurements of static respiratory mechanics during volume-controlled ventilation (VCV, *panel* **a**) and pressure-controlled ventilation (PCV, *panel* **b**). P_{aw} airway pressure, P_{alv} alveolar pressure P_{plat} plateau pressure, *PEEP* positive end-expiratory pressure, *PEEPi* intrinsic PEEP, *EIO* end-inspiratory occlusion, *EEO* end-expiratory occlusion

caused by circuit disconnection. Nowadays, several ventilators offer tools to perform automated $P-V$ curves (Fig. 4.4a), usually with a constant inspiratory flow ≤5 L/min after a prolonged expiration. The low inspiratory flow minimizes the resistive pressure, thus allowing a close estimate of the elastic pressure, in a patient sufficiently sedated or even paralyzed.

The $P-V$ curve may assume a sigmoidal shape in ARDS patients, with an upward concavity at low inflation pressures and a downward concavity at higher inflation pressures (Fig. 4.4a). Physiological studies in ARDS patients suggest risk of lung collapse at pressure levels below the "lower inflection point" (LIP) and excessive alveoli deformation (strain) above the "upper inflection point" (UIP) (Fig. 4.4a). Some studies suggest the use of $P-V$ curves to set the ventilator in a zone of high compliance, setting PEEP according to the LIP [10, 11]. However, there is no proof of the superiority of the $P-V$ curve method over other PEEP titration approaches, such as the decremental PEEP trial for maximum C_{rs}, use of positive end-expiratory transpulmonary pressure, and PEEP adjusted according to inspired oxygen fraction ($PEEP/F_iO_2$ table).

Recently, the low-flow $P-V$ curve has been described to identify complete airway closure [12] (Fig. 4.4b). The authors observed airway closure in approximately one-quarter of patients with moderate/severe ARDS under controlled mechanical ventilation. This finding indicates an increased risk of misinterpreting respiratory mechanics when PEEP is not enough to overcome the airway opening pressure.

4.6.3 Stress Index

The stress index (SI) is a value derived from the airway pressure vs. time curve during a constant inspiratory flow. Assuming that R_{rs} is constant during inspiration, the slope of the pressure-time signal can identify dynamic changes in C_{rs} along the increasing lung volume. The SI calculation is based on the following equation applied to P_{aw} vs. time curve:

$$P_{aw}(t) = a \times t^b + c, \tag{4.4}$$

where b is the SI parameter, which reflects the shape of the P_{aw} vs. time curve, a represents the slope of P_{aw} vs. time at $t = 1$ s, and the coefficient c is the pressure at $t = 0$ s. For values of coefficient $b<1$, the P_{aw} vs. time curve will present a downward concavity, indicating that compliance increases with time, whereas compliance decreases with time for values of coefficient $b>1$, producing an upward concavity. Value of the coefficient $b = 1$ indicates a straight P_{aw} vs. time relation and a constant compliance (Fig. 4.4c).

In an experimental model of ARDS, lungs ventilated with an SI range between 0.90–1.10 presented inflammatory biomarkers levels similar to those observed in non-ventilated lungs [13]. Although promising as a noninvasive approach to detect injurious lung patterns, SI use was limited in the past due to the necessity of dedicated software. However, a recent study found a good sensitivity and specificity using visual inspection to detect downward and upward concavity [14].

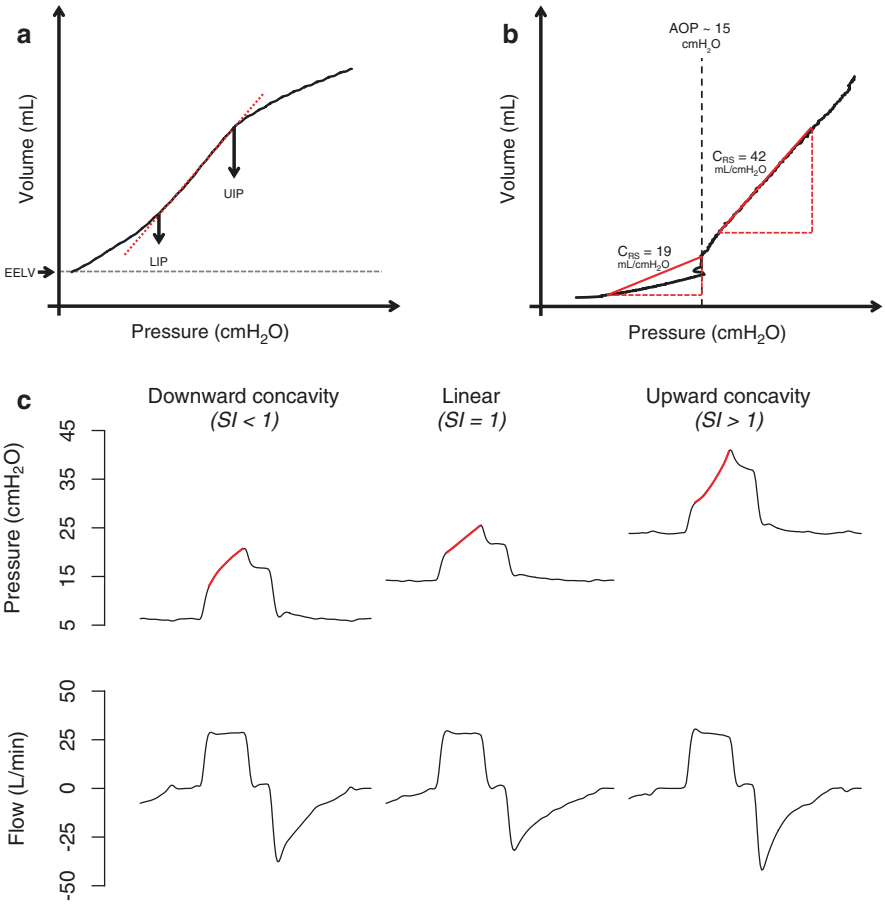

Fig. 4.4 (**a**) The pressure-volume curve of a model with acute respiratory distress syndrome (ARDS). The lower inflection point (LIP) and the upper inflection point (UIP) are defined by where the curve first begins to deviate from the maximum compliance line (red dashed line). (**b**) Low-flow inflation pressure-volume curve in a model with airway closure. Note the extremely low slope at the beginning of the $P - V$ curve, followed by an abrupt change in compliance above an airway opening pressure (AOP) ~15 cmH_2O. The airway closure phenomenon can lead to an erroneous calculation of respiratory system compliance (C_{rs}). (**c**) Illustration of the dynamic pressure-time curves with a fixed inspiratory flow. Left, the downward concavity (stress index [SI] < 1) indicates recruitment during the breath. Center, the linear relationship between pressure and time (SI = 1), suggests no recruitment or overdistension. Right, the upward concavity (SI > 1) indicates overdistension during the breath

4.7 Conclusion

With a good understanding of controlled modes and its implications, PCV and VCV are very similar during passive ventilation. However, if muscle effort occurs, these modes present substantially different features, which can impact patient comfort

and transpulmonary pressure applied onto the lungs. Despite evidence mainly showing clinical equivalence between PCV and VCV during controlled ventilation, ongoing research focusing on patient-ventilator interaction and monitoring of spontaneous breathing during mechanical ventilation could bring new insight regarding differences between these modes.

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Assisted Ventilation: Pressure Support and Bilevel Ventilation Modes

5

Irene Telias, Annemijn Jonkman, and Nuttapol Rittayamai

5.1 Introduction

In contrast to fully controlled mechanical ventilation, during assisted ventilation both the ventilator and respiratory muscles provide forces to move air into the lungs: the total pressure applied to the respiratory system (Ptot) equals the sum of the ventilator pressure (Pvent; or airway pressure, Paw) and the respiratory muscle pressure (Pmus). Therefore, tidal volumes are determined by both the ventilator settings and patient factors. Safely applying assisted modes at the bedside requires an understanding of their principles of operation, physiological effects, potential benefits and risks, and patient–ventilator interactions. In this chapter we will address these topics for pressure support ventilation (PSV) and bilevel ventilation modes during assisted ventilation.

I. Telias (✉)
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Division of Respirology, Department of Medicine, University Health Network and Sinai Health System, Toronto, ON, Canada

Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

A. Jonkman
Department of Intensive Care Medicine, Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands

N. Rittayamai
Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Salaya, Thailand
e-mail: nuttapol.rit@mahidol.ac.th

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5.2 Pressure Support Ventilation

5.2.1 Epidemiology, Potential Advantages and Disadvantages

Pressure support ventilation (PSV) is a spontaneous mode of ventilation limited by pressure and cycled by flow. Its use has increased since its initial description and it is, probably, the spontaneous ventilation mode most frequently used. Although PSV was introduced as a weaning mode, it is also often used in the acute phase. In an international cohort study, at least 10% of the patients were on a spontaneous ventilation mode already during the first 2 days of mechanical ventilation, being PSV the most frequently used [1].

PSV unloads the respiratory pump while maintaining some muscle activity. The patient has some control over tidal volume, inspiratory time, inspiratory flow, and respiratory rate contributing to his or her comfort. However, since the same ventilator pressure is delivered for every breath, independent of patient effort and metabolic needs, it also imposes several risks because of insufficient or excessive unloading. For this reason, understanding PSV operational principles and how to safely adjust ventilator settings while monitoring the patient's response is key.

5.2.2 Principles of Operation and Physiological Consequences of PSV

5.2.2.1 Trigger Sensitivity, Inspiratory Rise Time, Pressure Support Level, and Cycling-Off Criteria

During PSV all inspiratory efforts should be followed by ventilator's insufflation. Hence, the higher the patient's respiratory rate, the higher the rate of mechanical support from the ventilator and vice versa. Delivery of the level and timing of ventilator assist depends on various settings that can be modulated by the clinician on most ventilators, including the trigger sensitivity, inspiratory rise time, the level of pressure support, and the cycling-off criterion (Fig. 5.1a).

Patient effort is detected by the ventilator using a flow or pressure sensor according to the **trigger sensitivity** set by the user. Modern ventilators have a fast response with trigger delays lower than 100 ms [2]. Once the breathing cycle is initiated, the ventilator responds by providing a high inspiratory flow, which then gradually decreases throughout the inspiratory cycle. The **inspiratory rise time** determines how fast the peak inspiratory flow, and thus the peak airway pressure, is reached. Inspiratory rise time should be short since faster pressurization improves patient comfort and decreases work of breathing. Default is usually 150 ms, and changes to this setting are rarely made or meaningful. The **pressure support level** is the fixed amount of pressure above PEEP set by the clinician and delivered by the ventilator for each cycle.

Cycling to expiration occurs when the flow reaches a percentage of the peak flow (%peak flow). Default value for many ventilators is 25%, but, in most ventilators, this can be adjusted from as low as 1% to as high as 80% resulting in longer

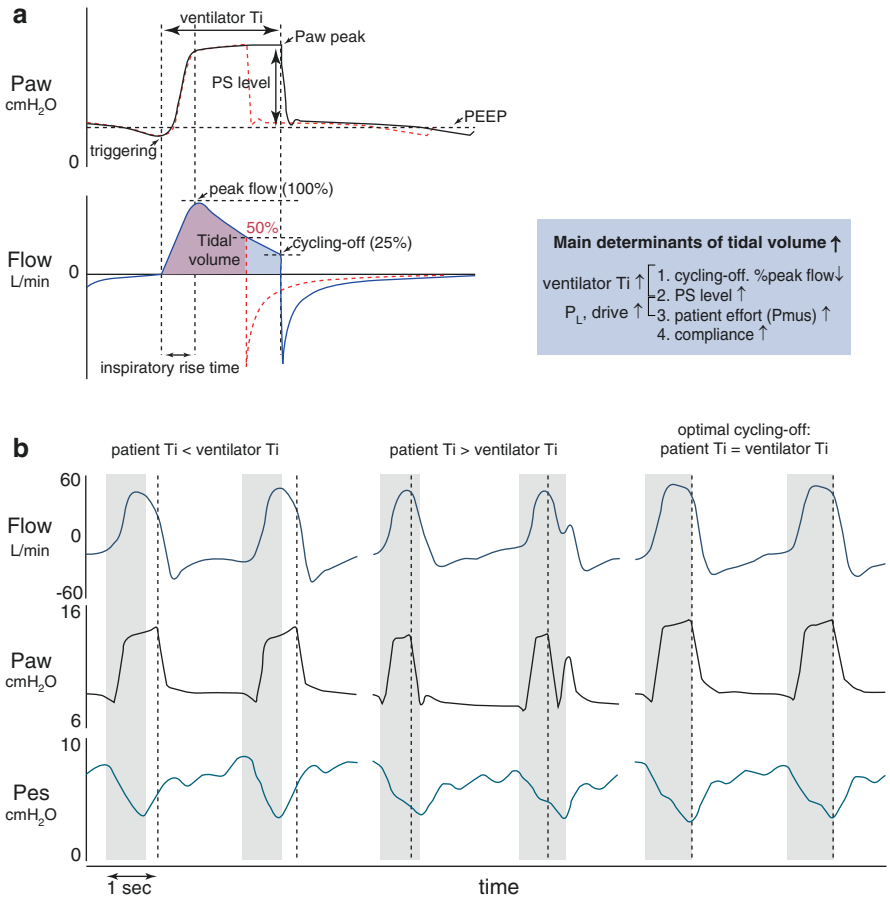

Fig. 5.1 Principles of operation and relationship between ventilator's insufflation time and patient's inspiratory time. (**a**) Basic characteristics of the airway pressure (Paw) and flow signal during pressure support ventilation (PSV) and the single effect of adjusting the cycling-off criterion (increasing %peak flow) on the resulting tidal volume. PS level: set pressure support level, i.e., the ventilator pressure that is delivered above positive end-expiratory pressure (PEEP) for each triggered breath. Inspiratory rise time refers to the time from start of inspiratory flow until peak flow (and thus, peak Paw) is reached. Adjusting the cycling-off criterion by increasing %peak flow (red dashed curves) results in a shorter ventilator insufflation time (Ti) and thus lower tidal volume. During PSV, tidal volume is determined by both ventilator settings (i.e., cycling-off criterion and PS level) and patient factors (i.e., patient muscular effort -Pmus- and respiratory system compliance). The PS level and Pmus together determine the transpulmonary driving pressure (P_L,drive), whereas the cycling-off criterion together with the PS level mainly determines the ventilator insufflation time (ventilator Ti), influenced by strength and timing of inspiratory effort. (**b**) Demonstration of the mismatch between patient neural inspiratory time (patient Ti) and ventilator Ti during PSV (left, middle), and an example where cycling-off matches patient's Ti (right). Dashed vertical line: end of ventilator Ti; gray area: patient Ti, with end of inspiration set at the nadir in esophageal pressure (Pes) to illustrate the effects of various cycling-off settings (note that the exact definition of patient Ti is debatable)

and shorter insufflation times, respectively. Ventilators have additional safety criteria for cycling to expiration in the context of expiratory muscle activity and leaks. Adjusting the cycling-off criterion allows to adjust insufflation times to better match the patient's neural inspiratory time avoiding short and prolonged cycling (Fig. 5.1b). Specifically, a higher %peak flow is beneficial for patients with obstructive pulmonary diseases resulting in longer expiration and avoiding hyperinflation.

5.2.2.2 Determinants of Ventilation and Impact on Breathing Pattern

The combination of ventilator settings and patient factors (primarily breathing effort and respiratory system compliance) impact the tidal volume, insufflation time, and thus minute ventilation. For instance, a higher support level, lower %peak flow, higher breathing effort, and better respiratory system compliance results in larger tidal volumes (Fig. 5.1a). Higher support levels also result in longer insufflation times. Conversely, the lower the level of support and breathing effort, and the higher the %peak flow, the lower the tidal volume.

There is also an impact of ventilator settings during PSV on the patient's breathing pattern. Higher support results in a decrease in inspiratory effort and shortening of neural inspiratory time in most patients [3]. Since higher support also prolongs ventilator insufflation time, a mismatch between a shorter neural inspiration and longer ventilator insufflation is frequent during high assist (i.e., prolonged cycling).

5.2.3 Potentially Injurious Patient–Ventilator Interactions During Pressure Support Ventilation

5.2.3.1 Over-Assistance with Ineffective Efforts and Apnea Events

Over-assistance occurs when there is ventilator support in excess compared to the patient's needs. It often appears during the recovery phase, when metabolic needs decrease and respiratory mechanics improve, resulting in several, frequently unnoticed, adverse consequences. First, patients can perform the minimal effort necessary to trigger the ventilator and then be passively insufflated for the remainder of the cycle with the risk of diaphragmatic atrophy. This occurs because during PSV, different than during proportional modes, there is always a substantial tidal volume delivered despite minimal patient effort (depending on the PSV level and respiratory system compliance).

Second, when inspiratory efforts decrease substantially, ineffective efforts may occur, especially with airflow obstruction (Fig. 5.2a). These occur because neural inspiratory time shortens, and the next inspiratory effort starts before complete exhalation. In the context of intrinsic PEEP these small efforts are unable to trigger the ventilator during the expiratory phase [4] . The result is that the observed respiratory rate is lower than the rate of patient's effort. The most effective strategy to eliminate ineffective efforts is to decrease the level of support [5]. However, clinicians need to be aware that after the level of support is decreased in this context, the respiratory rate increases substantially (often even doubles) and tidal volume decreases reflecting the patient's own breathing pattern; this should not be

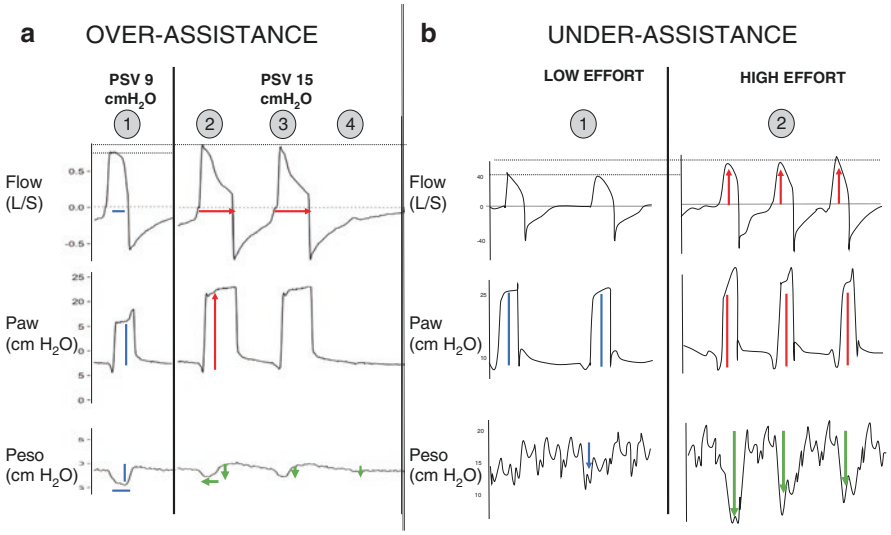

Fig. 5.2 Mechanisms and physiological consequences of over-assistance and under-assistance during PSV. (**a**) Flow, airway pressure (Paw), and esophageal pressure (Peso) signals over time for the same patient during lower levels of assist (pressure support -PSV- 9 cmH_2O) on the left (1) and higher assist (increasing PS to 15 cmH_2O) on the right (2-3-4). Increasing levels of assist result in an increase in peak flow, insufflation time (red arrow) (2), and tidal volume (not shown). Increasing assist generates a decrease in inspiratory effort and inspiratory time in most patients (seen by the smaller and shorter negative deflection in Peso—green arrow) (3). Overassistance can result in ineffective efforts (4) with a small inspiratory effort (green arrow) during mechanical exhalation not strong enough to trigger a ventilator insufflation. (**b**) Flow, Paw, and Peso signals in a patient with lower inspiratory effort on the left panel (1) and increased inspiratory effort on the right panel (2). Increased inspiratory can occur in the context of higher metabolic demands due to a new infection. During PSV, level of support remains constant despite higher effort. Stronger effort can be seen by the negative deflection in Peso (green arrow) resulting in higher peak flow (red arrow), higher tidal volume (not shown), and scooping in the Paw tracing (red line) known as flow starvation. Under-assistance can perpetuate high respiratory drive and have adverse consequences for the lung and diaphragm

interpreted as a sign of failure. Lastly, over-assistance can lead to apnea events during sleep because CO_2 falls below the apnea threshold resulting in arousals, awakenings, and sleep fragmentation [6]. This can also lead to a misconception of the lack of readiness to wean when, in fact, these apnea events are a consequence of excessive support.

5.2.3.2 Under-Assistance Leading to Flow Starvation and Double Triggering

Conversely, insufficient assistance during PSV (Fig. 5.2b) in the context of excessive respiratory drive and inspiratory effort results in potential injury to the lung through excess stress and strain due to high lung distending pressures [7]. Importantly, insufficient support can lead to flow starvation and dyspnea, perpetuating high respiratory drive. Additionally, when inspiratory efforts are strong enough,

double triggering occurs resulting in insufflation with larger tidal volumes. Specifically, PSV, different than proportional modes, is unable to adapt to an increase in ventilatory demands and, therefore it is important to adjust ventilator settings when conditions change.

5.2.4 How to Set the Level of Support to Prevent Over and Under-Assistance

Traditionally, the level of support has been set based on the observed tidal volume, lack of accessory respiratory muscle use, and respiratory rate. Initial studies targeted 8–12 mL/kg for tidal volumes. However, aiming for lower tidal volumes (6 mL/kg) is preferable to avoid over-assistance [5] and was associated with better gas exchange (higher lung diffusion for carbon monoxide) [8]. Clinicians should not aim for normalizing respiratory rate. Critically ill patients usually have a higher resting respiratory rate. In fact, a respiratory rate lower than 12 breaths/minute during PSV is indicative of over-assistance and should be avoided [9]. A rate lower than 30 breaths/minute was found to be predictive of a pressure-time product per minute less than 125 cmH_2O s/min (intermediate-low effort [10]), highlighting that a higher respiratory rate on PSV is preferable to ensure physiological respiratory muscle activity.

A modern approach for titration of PSV should incorporate measures of respiratory drive and effort. Monitoring techniques such as P0.1, occlusion pressure (Pocc), diaphragm ultrasound, esophageal pressure, or electrical activity of the diaphragm can be implemented into the clinical decision process and are discussed in Chap. 6. However, finding the optimal balance between patient effort and the level and timing of ventilatory assist during PSV remains a challenge and target values based on different monitoring techniques are still uncertain. Current evidence suggests that an intermediate range of inspiratory effort and avoiding excessive driving transpulmonary pressures and large tidal volumes are preferable. Suggested ranges were presented recently [11].

5.3 Bilevel Ventilation Modes

5.3.1 Bilevel Vs. Other Pressure-Controlled Modes

Bilevel ventilation is a pressure-cycled, time-controlled, intermittent mandatory ventilation which allows unrestricted spontaneous breathing at any time using an active exhalation valve. Therefore, breathing effort can occur at different time points within the ventilator's insufflation-exhalation cycle as seen in Fig. 5.3a [12]. One of the advantages of Bilevel ventilation mode is that some degree of mandatory ventilation is always guaranteed even in the absence of any respiratory drive, but the patient may still spontaneously breathe. The ventilator delivers continuous positive airway pressure (CPAP) at two set levels including high CPAP level (P-high) and low CPAP level (P-low). In the absence of spontaneous breathing, this mode resembles pressure control (PC) ventilation and, when usual settings are in place, it can be

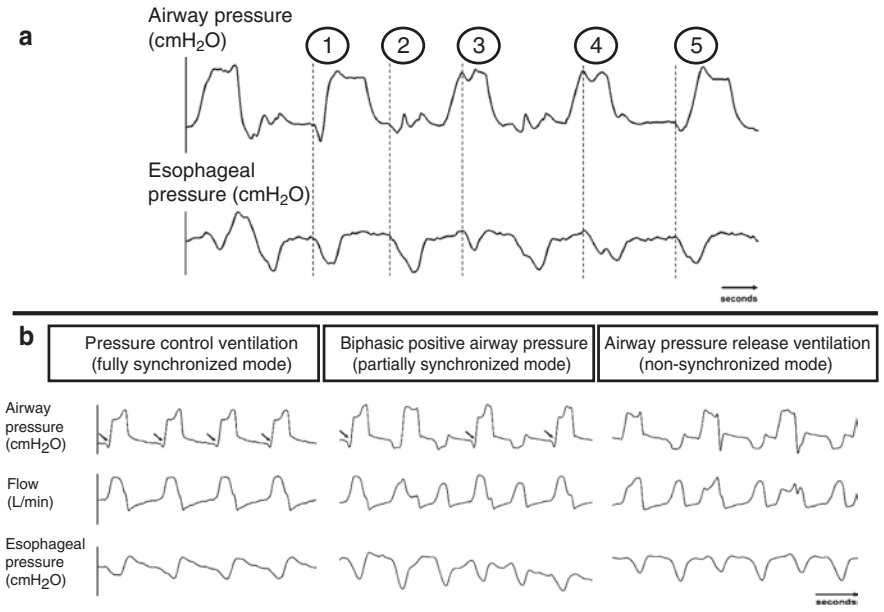

Fig. 5.3 (**a**) Types of breaths according to the timing within the ventilator's insufflation-exhalation cycle (1). Synchronized breath (2) Breathing at P-low (3) Breathing at P-high (4) Transition from P-high to P-low and (5) Transition from P-low to P-high. Dashed lines represent the beginning of each inspiratory effort. (**b**) Classification of pressure-controlled modes based on the degree of inspiratory synchronization. Black arrows represent the synchronization between patient inspiratory effort and ventilator breath

indistinguishable from PC inverse ratio ventilation (PC-IRV). When there is no breathing effort the ventilator insufflates air during the transition from P-low to P-high and exhalation occurs in the transition from P-high to P-low. Two types of bilevel ventilation are commonly used in clinical practice including BIPAP and APRV which can be classified according to the degree of inspiratory synchronization [13] and ventilator timing [14] as shown in Fig. 5.3b. However, many ventilator companies have their own specific nomenclature to refer to modes with similar characteristics (Table 5.1).

All pressure-controlled modes of ventilation, including bilevel ventilation modes, involve time-cycled changes between two pressure levels and can be classified according to the degree of synchronization with patient's inspiratory effort into fully synchronized, partially synchronized, and non-synchronized modes [13] (Fig. 5.3b). In fully synchronized modes assisted breaths are triggered with patient's spontaneous efforts. In partially synchronized modes, there is a synchronization time window allowing the patient to trigger an assisted breath within the time window. During these modes the patient can also take a breath without assistance outside the synchronization window. Finally, in non-synchronized modes, P-low and P-high are alternately delivered for fixed intervals and patient's spontaneous efforts are allowed at any time point; however, they do not trigger any additional pressure assistance.

Table 5.1 Nomenclature of pressure-controlled modes of ventilation according to the degree of inspiratory synchronization in common ventilator brands

Characteristics	Brands	Mode name
Fully-synchronized	Hamilton G5/S1	P-CMV
	Maquet Servo i/u	PC
	Drager Evita Infinity V500	PC-CMV
	Puritan Bennett 980	A/C PC
	GE Engström Carestation	PCV
	Vyaire AVEA/VELA	Pressure A/C
Partially synchronized	Hamilton G5/S1	DuoPAP
	Maquet Servo i/u	Bi-Vent
	Drager Evita Infinity V500	PC-SIMV+
	Puritan Bennett 980	BiLevel
	GE Engström Carestation	BiLevel (Trigger window—on)
	Vyaire AVEA/VELA	BiPhasic
Non-synchronized	Hamilton G5/S1	APRV
	Maquet Servo i/u	APRV
	Drager Evita Infinity V500	PC-APRV
	Puritan Bennett 980	BiLevel
	GE Engström Carestation	BiLevel (Trigger window—off)
	Vyaire AVEA/VELA	APRV

5.3.2 Physiologic Effects of Differences in Inspiratory Synchronization

Non-synchronized mode such as airway pressure release ventilation (APRV) and partially synchronized mode such as biphasic positive airway pressure (BIPAP) result in lower tidal volumes and transpulmonary pressure and more tidal volume variability than fully synchronized assisted pressure-controlled mode such as pressure control ventilation (PCV). In addition, non-synchronized modes also improve lung aeration by decreasing atelectasis in patients with acute respiratory distress syndrome (ARDS) compared to PSV [15–17]. However, patient's inspiratory effort increases significantly with non-synchronized and partially synchronized vs. fully synchronized pressure-controlled mode [12, 16].

5.3.3 Setting Bilevel Ventilation During Assisted Mechanical Ventilation

Ventilator settings for bilevel ventilation will vary from patient to patient. P-high is usually set according to the plateau pressure in a conventional mode; however, the general suggestion is to limit P-high <30 cmH_2O to avoid overdistention. P-low is frequently set at 0 cmH_2O and, because of the short time at P-low, auto-PEEP prevents alveolar collapse. Several studies were done setting P-high just below the upper inflection point and P-low just above the lower inflection point of the P–V

curve to prevent cyclic reopening/collapsing alveoli, however, other methods for P-low selection (similar to PEEP selection) are possible [17].

During the early phase of ventilation, longer inspiratory time (T-high) and shorter expiratory time (T-low) are commonly used during bilevel ventilation. The major difference between BIPAP and APRV is the time spent at P-high. A previous review study reported that extreme inspiratory:expiratory (I:E) ratio > 2:1 with the mean T-high of 3.4 ± 1.7 sec was frequently used in 46% of the studies using APRV, whereas I:E of 1:1 or mild inverse I:E (> 1:1 to <2:1) with the mean T-high of 2.4 ± 0.9 s was frequently used in BIPAP studies. Many ventilators also allow to add pressure support to assist spontaneous breathing every time the patient performs an inspiratory effort.

5.3.4 Clinical Evidence of Bilevel Vs. Conventional Modes During Assisted Mechanical Ventilation

Many randomized clinical studies compared bilevel ventilation with conventional ventilation strategy in patients with ARDS [18–20]. The results from a systematic review and meta-analysis also demonstrate that bilevel ventilation reduces duration of mechanical ventilation without any adverse effect on hemodynamics, and resulted in lower hospital mortality than conventional ventilation mode with low tidal volume strategy in some studies [21].

Bilevel ventilation has also been used in patients at risk for ARDS. A systematic review of observational data in high-risk trauma patients demonstrated that early application of bilevel ventilation may prevent progression of ARDS [22]. Furthermore, a randomized study in 63 trauma patients at risk for ARDS demonstrated that bilevel ventilation has similar outcomes compared to conventional ventilation with low tidal volume strategy [23].

5.4 Conclusion

During assisted ventilation both the ventilator and respiratory muscles provide pressure to move air into the lungs. Pressure support ventilation, the most frequently used assisted mode, allows to unload the respiratory muscle pump and it is comfortable for most patients. However, it provides a fixed ventilator pressure for each breath imposing the risk of over- and under-assistance with deleterious consequences that can be avoided by carefully adjusting ventilator settings while monitoring the patient. Bilevel ventilation is a pressure-cycled, time-controlled, intermittent mandatory ventilation mode which allows unrestricted breathing at any time (non-synchronized). Partially synchronized and non-synchronized modes improve lung aeration in some patients but inspiratory effort can also significantly increase during these modes as compared to fully synchronized modes; therefore, careful selection of the adequate patient population is advisable.

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Monitoring the Patient During Assisted Ventilation

6

Alice Grassi, Irene Telias, and Giacomo Bellani

During Assisted Mechanical Ventilation, the work of breathing is shared between the patient's muscles and the ventilator. The steady advancement in technology over the last decades led to the development of several modes of Assisted Ventilation (see Chap. 5), primarily oriented towards improving the patient–ventilator interaction. Assisted ventilation may be applied at different stages of the disease: still in the acute phase, as a transition from controlled ventilation, later on in the weaning phase or chronically.

Allowing a patient to breath spontaneously, while invasively ventilated, has some obvious physiological advantages and it is a step towards re-establishing a completely normal respiratory physiology, when all the work of breathing is supported by the patient's respiratory muscles. Assisted ventilation, as compared to fully controlled ventilation, is associated with decreased sedation requirement (clearly avoiding muscle paralysis) [1], preserved diaphragmatic trophism and prevention of

A. Grassi
Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada

I. Telias
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Division of Respirology, Department of Medicine, University Health Network and Sinai Health System, Toronto, ON, Canada

Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

G. Bellani (✉)
School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, ASST Monza, San Gerardo Hospital, Monza, Italy
e-mail: giacomo.bellani1@unimib.it

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dysfunction [2, 3]. On the other side, assisted ventilation, not differently from controlled ventilation, can expose the lung parenchyma to excessive stress and strain, leading to lung injury, but with some peculiar mechanisms, which led to the concept of "Patient Self-Inflicted Lung Injury" [4]. The deleterious effects of vigorous inspiratory efforts on lung parenchyma can be summarized as follows [5]:

1. Delivery of high tidal volumes, not completely under control of the clinician,
2. Local overdistension in the diaphragmatic regions due to pendelluft phenomenon,
3. Increase of transmural vascular pressure with increased risk of pulmonary edema,
4. Asynchronies, especially breath stacking causing overdistension.

Outside the lung, preliminary evidences are showing that diaphragm injury can occur not only due to inactivity but also to over activity and/or eccentric contraction (myotrauma) [3].

Finally, the changes in intrathoracic pressures due to mechanical insufflation associated to inspiratory efforts can lead, on one hand to improved preload, but, at the same time increased ventricular afterload, with a balance between favorable and adverse hemodynamic effects [6].

Assisted ventilation is very delicate, especially in patients with compromised lungs and it is hence clear how monitoring all the components involved is crucial to take advantage of the benefits while avoiding the risks.

6.1 Inspiratory Effort

Monitoring the inspiratory effort generated by the patient during assisted ventilation serves multiple purposes. First, it can give an indication of adequacy of the level of respiratory support and of sedation. Second, the change in respiratory effort during a trial of weaning from the ventilator may help in predicting the failure or success of such a trial [7]. Third, an insufficient or excessive level of inspiratory effort is related to diaphragm atrophy or dysfunction [3]. Fourth, in conditions of hemodynamic compromise, the effort done by the inspiratory muscles can be a significant source of oxygen consumption and therefore should be reduced by means of sedation and/or paralysis [8, 9]. Finally, it allows the calculation of the total pressure applied to the respiratory system, as described more in detail in the following.

6.1.1 Esophageal Pressure Derived Measurements

The measurement of the total work of breathing (WOB) requires an esophageal pressure (Pes) catheter. While the mechanical WOB is formally calculated as the area enclosed in a pressure–volume loop of the respiratory cycle (Campbell diagram, Fig. 6.1a), this does not account for the isometric contraction of the respiratory muscles and the duration of the effort. This limitation is overcome by the

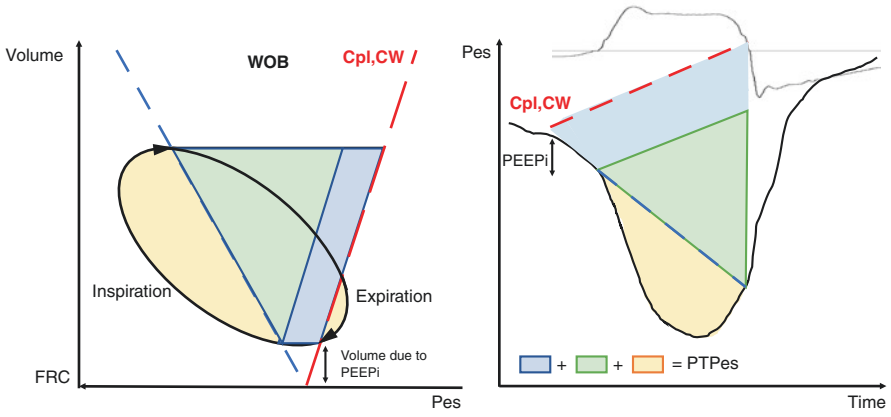

Fig. 6.1 The left panel shows the Campbell diagram of esophageal pressure plotted with lung volume. The intrinsic PEEP (PEEPi) is the pressure generated without generating any inspiratory volume. The work of breathing (WOB) is the integral of Muscle Pressure (Pmus). The red dashed line represents the passive recoil of the chest wall. The WOB has three components: resistive (yellow area during the inspiration phase), elastic (green area), and related to PEEPi (blue area). The small yellow area in the expiration phase represents the active expiratory WOB. The right panel shows the Pressure Time Product (PTP), which is the area under Pmus over the inspiratory time. As the WOB, the PTPes has three different components: resistive (yellow), elastic (green), and due to PEEPi (blue). The PTP is calculated in the inspiratory phase, i.e. between the two points with zero flow. Flow tracing is shown above Pes

esophageal Pressure Time Product (PTPes), which is the integral of the muscular pressure (Pmus) over time (Fig. 6.1b), which correlates well with the energy spent by the inspiratory muscles. Pmus is measured as the difference between the static recoil pressure of the chest wall and the total Pes. Normal values are between 50 and 150 cmH_2O*s/min [10].

Despite being less accurate and more simplistic than WOB or PTPes, estimating the inspiratory effort by Pes swing (maximum inspiratory deflection of Pes starting from end expiration) is more feasible at the bedside. Targeting a normal value of maximal inspiratory Pmus of 5 to 10 cmH_2O (which, with normally low chest wall elastance, corresponds to a Pes swing of 3 to 8 cmH_2O) seems reasonable to avoid excessive lung stress and diaphragm atrophy [11]. A recent study aimed at finding predictors of non-invasive ventilation success or failure, showed that intubation was avoided in those patients in whom the application of non-invasive ventilation led to a significant reduction of Pes swing towards more "physiological" values [12].

6.1.2 Tidal Volume and Respiratory Rate

Respiratory rate and tidal volume are poor estimates of effort in ventilated patients. They are influenced by respiratory mechanics and respiratory muscle weakness. Also, resting respiratory rate in critically ill subjects is high, does not follow

respiratory drive within a wide range ($PaCO_2$ from 23 to 45 mmHg) [13], and is independently modified by other factors [14, 15].

Nonetheless, a respiratory rate lower than 17 during pressure support can diagnose low drive and effort [16]. Increase in tidal volume without changing support reflects higher effort. However, a decrease in effort is not followed by a decrease in tidal volume below a certain threshold during pressure support. The Rapid Shallow Breathing Index (RSBI) combines these variables describing patient's breathing pattern. It was developed [17] for early prediction of weaning failure during a spontaneous breathing trial on T-piece (value >105 breaths/min/L) and suggestive of a fatiguing breathing pattern [18].

6.1.3 p0.1

The p0.1 is the drop in pressure generated by the patient in the first 100 ms of an inspiratory effort, during a short airway occlusion. It is an estimate of the patient's central respiratory drive, because there is no reaction to the mechanical load at the very beginning of an expiratory hold. Moreover, it is independent from airway resistances, because it is measured with zero air flow. Given the inter-breath variability of p0.1, an average of 3–4 measurements should be taken for a correct representation of respiratory drive. P0.1 in healthy subjects is between 0.5 and 1.5 cmH_2O [19]. One of the advantages of p0.1 is that it is easily measured by most of the available ICU ventilators either on a breath-to-breath basis (possibly underestimating the real value with large inspiratory efforts) or with a brief expiratory hold. A recent study [20] validated the p0.1 as measured by the commercial ventilators and confirmed its role as a measure of the patient's respiratory drive and work of breathing. Particularly, a threshold of 1 cmH_2O is used to determine a low inspiratory effort (PTP/min < 50 cmH_2O*s/min), while a value of p0.1 higher than 3.5 to 4 cmH_2O corresponds to a high inspiratory effort (PTP/min > 200 to 300 cmH_2O*s/min). Despite no value of high or low p0.1 was clearly correlated to weaning failure, these thresholds can be used in clinical practice to follow the responses in patients' efforts to change in respiratory support [20].

6.1.4 Occlusion Pressure

Another indication about the inspiratory effort can be obtained from the inspiratory depression of the airway pressure trace during a longer (as compared to p0.1) expiratory hold (ΔPocc), as shown in Fig. 6.2a. From ΔPocc, an accurate prediction of Pmus is possible through a simple calculation (Predicted Pmus = −3/4*ΔPocc). When performing this simple maneuver at the bedside, an average of three values should be calculated. The target of predicted Pmus for a safe ventilation is the same as for Pmus, 5–10 cmH_2O [21].

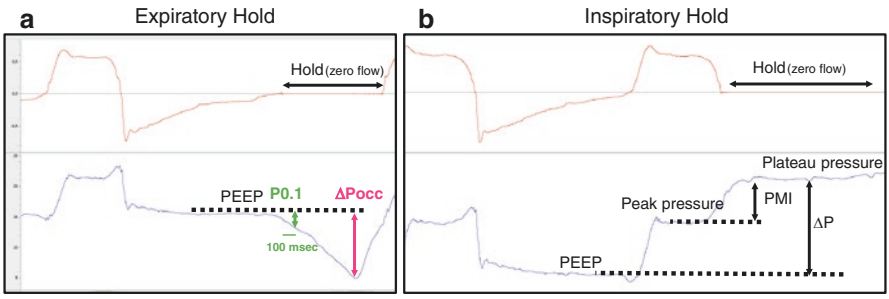

Fig. 6.2 Panel **a** shows an expiratory hold during pressure support ventilation. The expiratory occlusion pressure (ΔPocc) in pink is the difference between PEEP and the nadir of airway pressure during the hold. The airway occlusion pressure (P0.1) in green is the drop in airway pressure during the first 100 ms of the occlusion. Panel **b** shows an inspiratory hold during Pressure Support Ventilation. The airway pressure during the plateau is flat, the airflow is zero and therefore the plateau is readable. The measurement derived from an inspiratory hold are: Plateau Pressure, Pressure Muscle Index (PMI=Plateau minus Peak pressure), Driving Pressure (ΔP)

6.1.5 Pressure Muscle Index

Inspiratory effort can also be estimated through an inspiratory hold with a technique described in the 1990s [22, 23]. If, during the hold, the patient's respiratory muscles relax, the pressure that they were generating at end inspiration will be "released" inside the airways and, in a condition of zero flow, will appear as an additional pressure on the airway pressure tracing, in the form of a plateau pressure (Fig. 6.2b), which, as better outlined below, is required to be flat, in order to be "readable." The difference between the plateau and the peak pressure, the so-called Pressure Muscle Index (PMI), was shown to tightly correlate with the muscular pressure at end inspiration as measured by a Pes catheter [23].

6.1.6 Diaphragm Electrical Activity

The electrical activity of the crural diaphragm (Edi) can be monitored with a feeding tube arranged with eight electrodes on its distal end: while mainly devised to provide Neurally Adjusted Ventilatory Assist (Chap. 7), this is also a valuable monitoring tool. As compared to monitoring the flow and pressure tracings on the ventilator, the electrical activation of the diaphragm is obviously closer in time to the output of the respiratory centers, being a measure of respiratory drive [24]. Edi was shown to tightly correlate with transdiaphragmatic pressure and to change proportionally with the level of respiratory assist [25]. Eadi can be used to evaluate "graphically" the patient presence of asynchronies [26], intrinsic PEEP [27], reverse trigger [28] as also shown in Chap. 37. Moreover, it has been suggested that the ratio between the drop in airway pressure and Eadi during one expiratory occlusion (sometimes named Neuro-Muscular Efficiency) allows to translate the Edi value into Pmus during regular tidal ventilation [29], as depicted in Fig. 6.3.

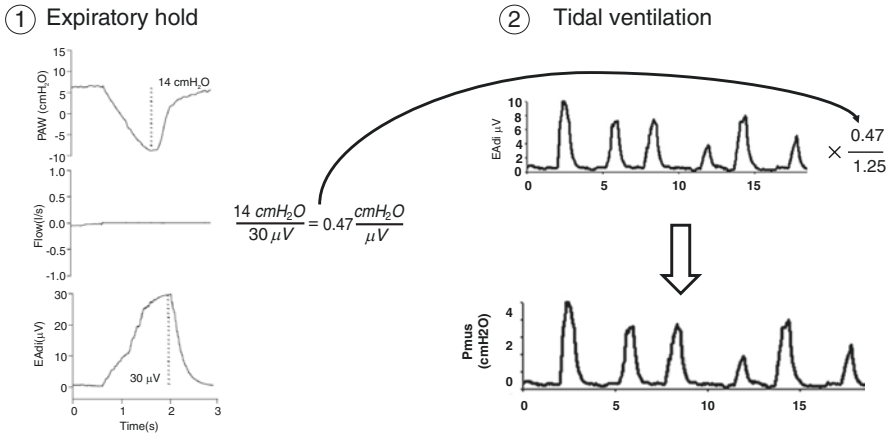

Fig. 6.3 Technique to obtain muscle pressure (Pmus) from Electrical Activity of the diaphragm (Eadi). At first (Panel 1) during an expiratory hold, compute the ratio between the pressure of the inspiratory effort and the Eadi amplitude corresponding to the swing. This ratio (named Neuromuscular Coupling or Pressure/Eadi Index, PEI) has dimensions of $cmH_2O/\mu V$ and is supposed to indicate the amount of pressure (in cmH_2O) that the respiratory muscles of the patients are generating for each microvolt of electrical activity. This ratio (divided by 1.25 to account for the more favorable contraction of the diaphragm during isometric contraction) is then used (Panel B) as a conversion factor, in the subsequent breaths to convert Eadi in Pmus

6.2 Total Pressure Distending the Respiratory System

During assisted ventilation, both the positive pressure imposed by the ventilator (set by the clinician) and the negative pressure generated by the patient's muscles contribute to overcome the resistive and elastic pressures of the respiratory system, leading to increase in lung volume. Hence considering only the pressures displayed on the ventilator screen (peak pressure and PEEP) does not provide a truthful representation.

The patient inspiratory effort determines the amount of negative pleural pressure generated in every breath, which "pulls" the alveoli from outside. A direct measurement of this pressure is provided by a Pes catheter, surrogating pleural pressure. Transpulmonary pressure (P_L) is the difference between Paw and Pes and it estimates the stress applied on the alveoli at any given moment. An experimental study [30] clearly showed that strong inspiratory efforts worsen lung injury despite limiting the positive pressure imposed by the mechanical ventilator to lower than 30 cmH_2O, demonstrating that a component of the pressure equation is hidden to the clinician only monitoring the instantaneous Paw shown by the ventilator.

Many factors though should be taken into consideration when using P_L as a measure for lung stress.

Dynamic P_L is the maximum P_L during an inspiratory effort. This value also includes the pressure generated to overcome the airflow resistance. While on one

hand the resistive component is not dissipated across the alveolar wall, it may lead to absolute negative value alveolar pressure, possibly injurious. Moreover, P_L is normally calculated under static conditions during controlled ventilation and this should be taken into account when comparing assisted versus controlled ventilation [31]. Finally, P_L is a global measurement and does not reflect regional differences in lung properties, which might lead to regional heterogeneity, as outlined below.

Safe limits for P_L during spontaneous breathing are not fully established yet, but a ΔP_L of 15 cmH_2O has been suggested as threshold not to be exceeded for a safer Assisted ventilation [11].

While the Pes catheter is the most direct way of estimating P_L, it must be recognized that its use in clinical practice is not widespread.

Alternative methods of estimating the total pressure distending the respiratory system have been developed, by means of the mechanical ventilator tracings.

The inspiratory hold described above, and shown in Fig. 6.2b as a means of measuring PMI reveals a plateau pressure which can be higher than the airway peak pressure, since it includes both the pressure generated by the ventilator plus the muscular pressure released by the inspiratory muscles [32–34]. This Plateau pressure has exactly the same meaning as when measured during controlled ventilation, allowing to compute static Driving Pressure (Plateau Pressure-PEEP). Intuitively, performing an inspiratory hold during Assisted ventilation is more complex and uncertain than in passive conditions, because the patient's muscles are active and the plateau would not be reliable in the absence of relaxation. Approximately 20% of patients will have unreadable traces during Assisted ventilation, especially the ones with higher respiratory drive [33, 34]. Safe limits for driving pressure during assisted ventilation are not established yet, but its correlation with outcome in a small retrospective study supports using the same threshold used in controlled ventilation (<15 cmH_2O, the lower the better) [35]. Even if some expiratory muscle activity cannot be excluded in the presence of a flat plateau [36], this would cause an over estimation of the driving pressure, which, if anything, leads to set a safer rather than less safe ventilation.

ΔPocc, the difference between PEEP and the lowest value of Paw reached during an expiratory hold (described above as a way of predicting Pmus), can be used also to estimate the transpulmonary dynamic driving pressure. This maneuver is technically easier to perform than the inspiratory hold, because it does not require any post hold interpretation of the ventilator trace. An estimation of transpulmonary dynamic driving pressure can be made through a calculation from ΔPocc:

Predicted Dynamic transpulmonary driving pressure = (Peak airway pressure – PEEP) – 2/3 ΔPocc.

The AUROC for this predicted pressure to estimate an excessive dynamic transpulmonary driving pressure was >0.9 [21].

It is important to keep in mind that the measurement of plateau pressure and of ΔPocc provide to the clinician complementary information, so measuring both of

them, especially in the absence of a Pes catheter, can allow a more complete description of the respiratory mechanics. Indeed, a recent study conducted in an experimental model of mild ARDS showed that a higher TV and DPaw, and not a higher dynamic driving pressure, were associated with worse lung and diaphragmatic injury [37].

6.3 Asynchronies

Asynchronies happen when the inspiratory and expiratory times of the patient and of the ventilator are partly or entirely not matched. Asynchronies are a common problem, affecting up to one-third of the patients [38], and a multicenter study (BEARDS, NCT03447288) specifically looking at the incidence of asynchronies during mechanical ventilation for ARDS is currently ongoing. Some studies showed an association between the incidence of asynchronies and outcomes (duration of mechanical ventilation, ICU mortality) [39–41]. While, on one side asynchronies might be a marker of more severe lung disease, and not a direct cause of worse outcomes, they can be associated with patient discomfort and cause an increase in the sedation administered [38]. It is important for the clinician at the bedside to recognize asynchronies when these happen and try to optimize the ventilator settings in order to reduce their incidence. Automated tools to recognize asynchronies and quantify their burden have been developed [42]. The most common asynchrony is ineffective triggering, occurring when the patient inspiratory effort fails to trigger the ventilator, because the pressure or flow generated by the muscles are not enough to overcome the trigger threshold. This can be a sign of muscle weakness or of the presence of intrinsic PEEP, which can be monitored either by Pes or Edi since, the presence of expiratory muscles activity does not allow to measure auto-PEEP through an expiratory hold during assisted ventilation. The decrease in Pes or the increase in Edi before the beginning of the inspiratory flow allow to estimate the amount of pressure that the inspiratory muscles have to overcome before being able to trigger the ventilator [27]. Another common asynchrony is double trigger or double cycling: this happens when the ventilator inspiratory time is shorter than the patient inspiratory time and the patient triggers another breath before a complete exhalation has happened [42]. It can cause the so-called breath stacking, meaning that the total tidal volume delivered is higher than intended and can lead to lung overdistension [43]. Lastly, auto-trigger is a breath delivered by the ventilator in the absence of patient's effort, triggered by cardiac oscillations or air leak. It can also lead to breath stacking. A more complete list of asynchronies can be found in [38]. The recognition of asynchronies is made easier in the presence of a Pes catheter or an Edi monitor. Both of them allow a direct visualization of the patient muscular activity, its intensity and its timing during the ventilator respiratory cycle [8–10]. In the absence of these monitors, the clinician should pay attention to the airway pressure and show waveforms on the ventilator, to identify the presence of asynchronies. Chapter 39 contains several images of asynchronies to allow the reader to familiarize more with this very common problem.

6.4 Distribution of Ventilation and Pendelluft

As already mentioned, Paw and Pes tracings allow a global monitoring of pressure distending the respiratory system, without discriminating between different regions. While normal lungs have a fluid-like behavior, with even distribution of the pressure generated by inspiratory muscles throughout the parenchyma, injured lungs show a "solid-like" behavior [44]. This means that some areas would not inflate and some other would be overdistended once exposed to the same distending pressure. As a consequence, a "pendelluft" phenomenon can develop as shown in Fig. 6.4. This is the movement of tidal volume inside the lung between zones with different time constants and it is not identified by the change in ventilator tracings nor by monitoring P_L. It can lead to regional overdistension of inflated lung regions [45, 46]. Electrical Impedance Tomography (EIT) is a bedside monitoring tool that allows to

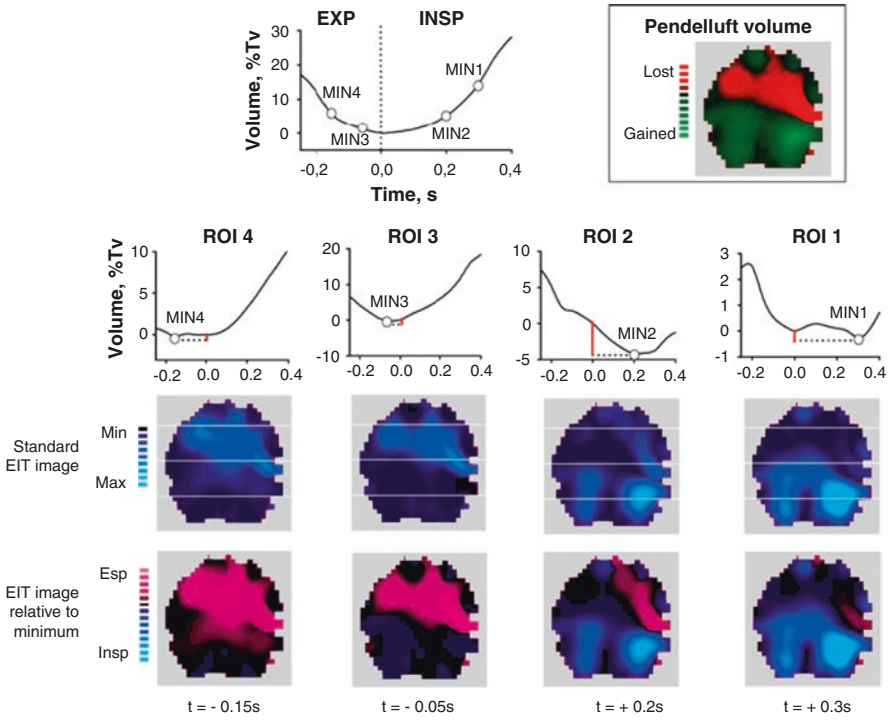

Fig. 6.4 Evidence of pendelluft in a patient during a weaning trial: dyssynchrony between different regions is noticed because of minimum impedance values (regional expiration) of the dorsal regions of interest (ROI 3 and 4) are reached during global expiration (EXP), while in the ventral ones (ROI 1 and 2) these are reached during inspiration (INSP). Hence, some gas volume (red bars) inflating ROI 3 and 4 came from the deflation of ROI 1 and 2: inspiration in the dorsal ROIs started when ventral ones were still expiring (expiration in purple color). Pendelluft gas moved from the ventral towards the dorsal lung regions (boxed image). (Reproduced under a Creative Commons Attribution 4.0 International License from [46])

visualize the differences in ventilation among different lung regions (see Chap. 33). EIT is the only monitor able to identify the presence of pendelluft phenomenon, visualized as the inflation of some lung regions while others are deflating [45]. This phenomenon was shown to increase with decreasing ventilatory support and is associated with ineffective ventilation and possible local overdistension [46]. Moreover, EIT may provide useful information in regard to changes in distribution of regional ventilation caused by breathing efforts [47].

6.5 Evaluation of Respiratory Muscles Activity by Ultrasound

Respiratory muscles ultrasound is a newer and rapidly evolving way to monitor the spontaneously breathing patients [48]. Diaphragm thickness and function have been extensively studied and also shown to correlate with outcome [2]. Taking advantage of the non-invasive and bedside availability of the technique, accessory inspiratory muscle and abdominal muscles have been the subject of more recent studies [49]. More details about respiratory muscles ultrasound are available in Chap. 32.

6.6 Conclusion

Several data, made available over the last decade, allow a better understanding of the benefits and risks inherent to allowing spontaneous breathing and the crucial role of patient's effort. In addition to esophageal pressure, several techniques are readily available at the bedside. A wider adoption of these in the clinical practice should proceed along with clinical research, defining the targets to prevent harm and improve patient's outcome.

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Neurally Adjusted Ventilatory Assist

7

Hadrien Rozé

7.1 Working Principles

For spontaneous breathing to occur, the impulse generated by the respiratory centers is transmitted through the phrenic nerve that stimulates the diaphragm, causing muscle contraction. As a result, the pressure in the airway drops causing an inflow of air into the lungs. The electrical activity of the diaphragm (EAdi) constitutes the temporo-spatial summation of motor-unit action potential, its amplitude relates to the changes in motor-unit firing rate and recruitment. The EAdi signal is synchronized and proportional to the neural drive [1]. Neurally adjusted ventilation assist (NAVA) is based on the recording of EAdi through an array of electrodes placed on a nasogastric catheter. The electrodes must be located at the level of the esophageal-gastric junction close to the muscle fibers crural diaphragmatic [2]. The EAdi signal is captured from the electrodes by the ventilator, and it will be used, in NAVA mode, to assist the patient's breathing in synchrony with, and in proportion to, the patient's respiratory drive. Hence NAVA will amplify the effort of the patient's respiratory muscle activity, providing the necessary support to improve the difficult imbalance between capacity and demand [3].

7.1.1 EAdi Signal

EAdi uses several bipolar electrodes in a sequential order with a specific processing technique that allow to take into account the displacement of the diaphragm. Most of the signal disturbances such as ECG, and artifacts are avoid by the processing of

H. Rozé (✉)
Thoracic Intensive Care Unit, Department of Anesthesiology and Critical Care, Bordeaux University Hospital, Bordeaux, France
e-mail: hadrien.roze@chu-bordeaux.fr

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the signal in order to display $\Delta EAdi_{(t)}$ as a waveform on the ventilator's screen synchronized with the other curves $P_{aw(t)}$, $Flow_{(t)}$, and $V_{T(t)}$ [4]. EAdi signal has been validated with numerous clinical studies showing that it is proportional to transdiaphragmatic pressure, and an increase of the level of ventilatory assistance decreases the pressure time product and EAdi in proportion [5, 6]. It is important to notice that EAdi is insensitive to recruitment of accessory muscles which can be activated to unload the diaphragm. With the neural feedback of the control of breathing, EAdi amplitude will increase with an inspiratory effort, a decrease of sedation, a reduction of the level of assist, or worsening respiratory condition.

If the EAdi catheter is functioning in the appropriate position in the esophagus, an EAdi amplitude of zero μV means that there is no diaphragmatic activation. When EAdi is used with non-proportional modes of ventilatory assistance (e.g. Pressure Support Ventilation), zero EAdi can be the consequence of over assistance, but also disturbed control of breathing with persistent sedation or phrenic nerve damage. Indeed it is possible to use EAdi with ventilatory modes other than NAVA as a monitoring tool, in order to improve patient–ventilator interaction [7].

7.1.2 NAVA Mode

7.1.2.1 Trigger Under NAVA

Trigger threshold is electrical (in μvolt) instead of pneumatic (pressure or flow). As shown on the Fig. 7.1, NAVA will follow the neural drive represented by the EAdi waveform to start and terminate insufflation. Inspiratory trigger starts insufflation when ΔEAdi is >0.5 μvolt and expiratory trigger stops insufflation and begins expiration when EAdi decreases to 70% of the EAdi peak (this parameter cannot be changed). For each cycle, inspiratory trigger is electrical with EAdi, but flow-based pneumatic trigger may occur if this is earlier than EAdi, since the rule between the two triggers is first come—first served. In case of a long neural inspiration the breath is cycled off when inspiratory time reaches 2.5 s.

7.1.2.2 The Level of Assist

The level of pressure delivered by the ventilator during inspiration is proportional to the variation of EAdi (ΔEAdi) which is multiplied by a proportionality factor termed $NAVA_{level}$ in $cmH_2O/\mu volt$ (equation below).

$$P_{aw(t)} = PEEP + NAVA_{level} \times \Delta EAdi_{(t)}$$

The waveform of the airway pressure will be the same as the waveform of EAdi but the proportionality can be increased or reduced with the $NAVA_{level}$.

The $NAVA_{level}$ is set manually in a range between 0.1 and 15 $cmH_2O/\mu volt$ (in 0.1 or 0.2 $cmH_2O/\mu volt$ steps). In clinical practice levels below 3 $cmH_2O/\mu volt$ are typically used. The effect of $NAVA_{level}$ on P_{aw} depends on $EAdi_{peak}$, since an $EAdi_{peak}$ at 30 μvolts will deliver much more pressure if $NAVA_{level}$ is doubled than if $EAdi_{peak}$ is 5 μvolts. For safety, upper pressure limits are applied during NAVA and P_{aw} cannot exceed a value 5 cmH_2O lower than airway pressure alarm limit (Fig. 7.1).

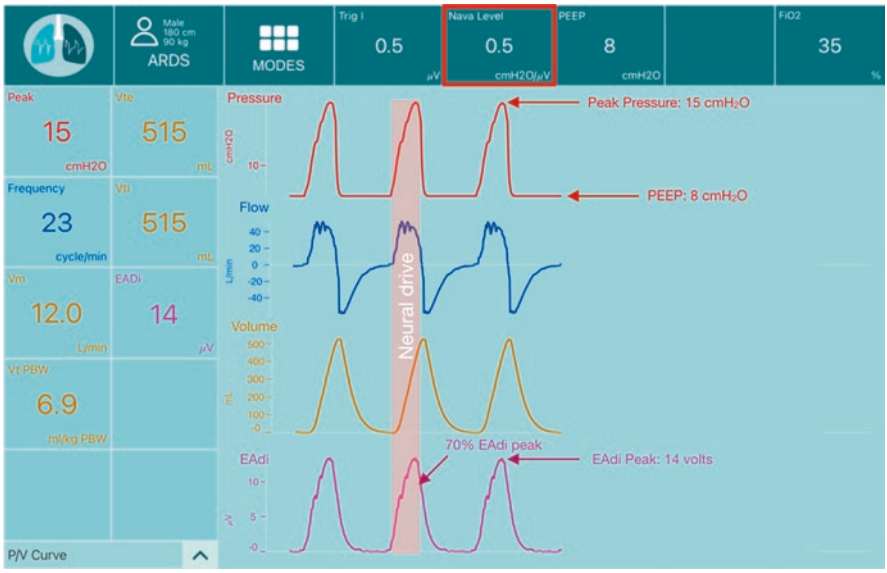

Fig. 7.1 This figure illustrates the synchronization of pressure and flow delivery with EAdi, starting from 0.5 µvolt and stopping insufflation when EAdi = 0.7 × 14 = 9.8 µvolts. The level of peak pressure delivered by the ventilator is the consequence of the peak EAdi at 14 µvolts, the PEEP at 8 cmH_2O and the $NAVA_{level}$ at 0.5 cmH_2O/µvolt. So Peak Pressure = 8 + 0.5 × 14 = 15 cmH_2O. A $NAVA_{level}$ increases to 1 cmH_2O/µvolt will increase pressure assist, the Peak Pressure will be 8 + 1 × 14 = 22 cmH_2O and after it will change in proportion to EAdi. (Figure from the application iVentilate. Courtesy of Pr Hadrien Rozé)

A change of $NAVA_{level}$ will change the amplitude of assistance in relation to EAdi, as shown on the Fig. 7.2. Starting from the lowest level an increase of the $NAVA_{level}$ will increase the pressure delivered by the ventilator, and the neural feedback of the control of breathing will reduce EAdi hence reducing the pressure delivered (Fig. 7.2) [6, 8].

7.2 How to Set Ventilatory Assistance During NAVA

There are different methods to set $NAVA_{level}$ based on different assessments of respiratory physiology, taking advantage of the effect $NAVA_{level}$ titration on respiratory mechanics and/or neural feedback [9].

7.2.1 Airway Pressure Targets

Before switching an actively breathing patient to NAVA, it is possible to use the "NAVA preview." This function estimates and displays the airway pressure which would be delivered during NAVA in a patient under another ventilatory mode

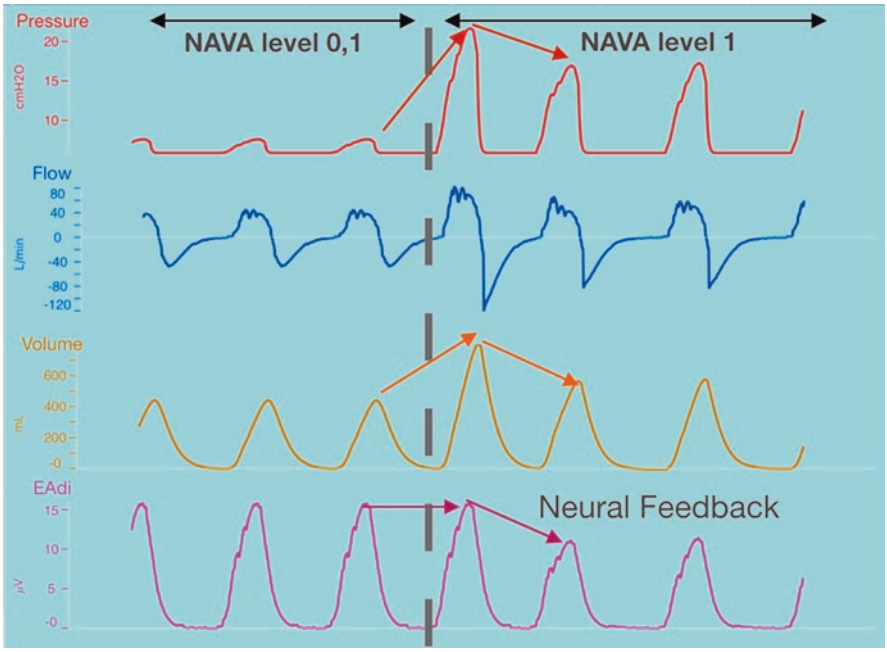

Fig. 7.2 This figure illustrates the effect of increasing $NAVA_{level}$ from 0.1 to 1 cmH_2O/µvolt on the neural feedback with a corresponding decrease of EAdi from 17 to 12 µvolts and airway pressure from 22 to 17 cmH_2O. (Figure from the application iVentilate. Courtesy of Pr Hadrien Rozé)

(e.g. pressure support). The $NAVA_{level}$ may be titrated until both peak P_{aw} match. This assumes that the current level of assistance is optimal for the patient. P_{aw} peak matching does not guarantee similar assist levels due to differences in P_{aw} profile. NAVA pressure time waveform is not square as in most pressure-targeted modes, so another possibility is to match mean airway pressure [10]. The breath-by-breath variability in EAdi amplitude under NAVA may make matching difficult. Finally, once switched to NAVA, the level of EAdi (and hence of P_{aw}) might change due to neural feedback.

7.2.2 Tidal Volume Response to $NAVA_{level}$ Titration

If the patient is in respiratory failure without any assist, it is possible to assess the changes in P_{aw} and tidal volumes (V_T) during a stepwise increase in $NAVA_{level}$. A two-phased response can be observed:

– *First response:* increase in $NAVA_{level}$ results in a steep increase in both P_{aw} and V_T until further increase in $NAVA_{level}$ results in less P_{aw} increase and no change in V_T (second response).

– *Second response*: it indicates a "comfort zone" where assist levels are adequate to sufficiently unload the respiratory muscles, further increase in $NAVA_{level}$ do not increase V_T because neural feedback reduces EAdi. The optimal $NAVA_{level}$ is identified at the transition point, describing a change from the previously insufficient assistance to a level that meets the patient's respiratory demand, as indicated by a stable tidal volume [5]. A limitation of this method is that some patients do not demonstrate clearly these two phases during $NAVA_{level}$ titration.

7.2.3 EAdi Response to $NAVA_{level}$ Titration

This method has been proposed in patient suffering from respiratory failure without assistance following a failed spontaneous breathing trial (SBT), and it allows to assess the decrease in EAdi during a stepwise increase in $NAVA_{level}$.

The first step consists in recording the EAdi during the failed SBT ($EAdi_{maxSBT}$) corresponding to respiratory failure. The $NAVA_{level}$ titration will reduce EAdi to a "comfort zone." A reduction of EAdi amplitudes in order to have ~60% of the $EAdi_{maxSBT}$ was sufficient for difficult to wean patients [11]. This procedure can be repeated daily, allowing a progressive reduction of the $NAVA_{level}$ until successful SBT.

Another method aims to titrate $NAVA_{level}$ targeting a reduction of $EAdi_{peak}$ by 50% of the value recorded with the lowest $NAVA_{level}$ (0.1 $cmH_2O/\mu volt$). In a randomized controlled trial, this protocol with NAVA decreased significantly the duration of mechanical ventilation when compared to PSV [12].

7.2.4 Neuro-Ventilatory Efficiency (NVE)

The NVE (ration between tidal volume and EAdi, $mL/\mu V$) describes the capacity of the respiratory muscles to convert the EAdi to ventilation without ventilatory assistance [13]. NVE has been used to titrate $NAVA_{level}$ and less unloading was associated with greater diaphragm activity and improved ventilation in the dorsal dependent lung regions [14].

7.2.5 EAdi Derived Indices with NAVA

The patient–ventilator breath contribution (PVBC) index is defined as the ratio of inspiratory V_T to EAdi variation of an unassisted breath ($V_{T,insp}/\Delta EAdi$) to that of an assisted breath (figure below) [15]. PVBC values can range between 0 and 1 where 1 means that V_T is fully generated by the patient inspiratory effort. Interpretation must take into account absolute ventilator assist and patient effort (Fig. 7.3).

Fig. 7.3 This figure illustrates the comparison of neuro ventilatory efficiency (NVE = V_T/EAdi) between one assisted breath (NVE_{assist} = 667/10 = 66.7 mL/µV) and one unassisted ($NVE_{unassist}$ = 265/11 = 24 mL/µV). Patient Ventilator Breath Contribution = 100 × 24/66.7 = 36%. (Figure comes from the application iVentilate. Courtesy of Pr Hadrien Rozé)

7.3 How to Set PEEP Under NAVA

During NAVA, PEEP setting does not differ from other modes, but this might impact respiratory muscle load and function, and hence EAdi. NVE response to PEEP changes could allow to identify a PEEP level at which the EAdi required for V_T generation is minimized (i.e. highest NVE) [16].

EAdi with NAVA or PSV can be a tool (comparable to esophageal pressure) for monitoring the presence of intrinsic PEEP and the effects of the application of an external one [17]. Moreover, with NAVA the effort necessary to overcome intrinsic PEEP can be lower than during PSV, and be less affected by the decrease of PEEP [17]. Lastly, with PSV, EAdi can be used to set PEEP in order to reduce inspiratory trigger delay in case of intrinsic PEEP [7].

7.4 How to Wean NAVA

NAVA can be combined with any kind of weaning process, switching from NAVA to SBT with PSV or CPAP or other methods. If the patient is unable to pass the SBT, whatever the method, mechanical ventilation with NAVA is resumed and then it is possible to titrate again the $NAVA_{level}$ with the same protocol used at NAVA initiation. It has been shown that EAdi for a given level of pressure support can change

day after day between the first day under NAVA and the day of successful SBT [13]. It is possible, for example, in the beginning of the weaning process that EAdi for a given level of pressure assist is still decreased by residual sedation [18]. This daily assessment of EAdi for a given assist may help to set $NAVA_{level}$ accordingly. If there is no interaction with residual sedation, any improvement of the respiratory function may be characterized by a decrease of the neural drive (so a decrease of EAdi) and should be followed by a reduction of the $NAVA_{level}$.

Weaning process with NAVA could reduce the duration of mechanical ventilation as compared to PSV [12].

7.5 Clinical Effects of NAVA

7.5.1 Effect on V_T

In non-proportional modes (e.g. PSV) an increased level of assist is, almost invariably, associated with increasing V_T values [19] and a patient can simply trigger a breath with minimal effort, being passively insufflated afterwards. Moreover, the insufflation may continue while the patient has ceased the effort, without determining cycling off of the ventilator. In contrast, V_T tends to remain stable with NAVA, despite increasing $NAVA_{level}$, suggesting that NAVA can protect against the risk of overassistance and overdistension. Moreover, with NAVA insufflation stops when the output of the inspiratory centers to the diaphragm ends.

Increasing NAVA levels reduces EAdi, thereby self-limiting the increase in lung-distending pressures and volumes [6, 8, 20]. The Hering–Breuer reflex presumably plays a role in the control of V_T [21] but vagus inhibition in human is probably weak and does not change breathing patterns. Other non-chemical mechanisms involved in the control of V_T with afferents from upper airways in non-intubated patients, chest wall, and diaphragm are stimulated by stretching. This can explain why NAVA has been used successfully with protective V_T in lung transplanted patients with bilateral vagotomies [22]. Moreover, in comparison to PSV, NAVA allows a greater variability of the breathing pattern [20].

7.5.2 Effects on Asynchrony

Compared to PSV, NAVA especially may improve patient–ventilator synchrony, and overall patient–ventilator interactions [23] by reducing inspiratory trigger delay, expiratory time in excess, and the total number of asynchronies [24]. With NAVA ineffective efforts or delayed cycling may nearly disappear, which can be of particular relevance for patients with obstructive diseases [24, 25].

In patients with severe pulmonary restriction and low compliance, NAVA can be used to significantly reduce the number of asynchronies with premature cycling and double triggering even when an optimized expiratory trigger is used during PSV [26].

Neural-triggering under NAVA can also be useful in patients with bronchial fistulae and serious air leakage during mechanical ventilation. In that situation it might be necessary to fully decrease the pneumatic trigger sensitivity in order to use exclusively the neural trigger and avoid auto triggering [27].

7.5.3 NAVA During Non-Invasive Ventilation or Tracheostomy

Also during non-invasive ventilation, (NIV), NAVA improves patient–ventilator synchrony by reducing inspiratory trigger delay and severe asynchrony compared with PSV, with a drop in NAVA ineffective efforts, delayed and premature cycling [28]. NAVA-NIV instead of PSV improves patient–ventilator interaction, despite some studies did not employ specific NIV function for leak compensation. However, NAVA could improve patient–ventilator interaction more than the activation of a specific NIV algorithm during PSV, and the combination of NAVA with a specific NIV algorithm could offer the best compromise between a good patient–ventilator synchrony and a low level of leaks [29].

NIV-NAVA can be particularly interesting with a helmet interface. Because of the significant compressible volume of a helmet, patient's ventilator interaction can be difficult and NIV-NAVA could improve synchrony [30].

7.6 Limitation of NAVA

Clearly, NAVA cannot be used in the absence of respiratory drive and excessive sedation significantly reduces EAdi.

NAVA should be used cautiously in case of excessive respiratory drive since NAVA would amplify this. Proportional assist mode with NAVA and a high respiratory drive is at risk of patient self-inflicted lung injury. Moreover, it is important to choose the right method to set $NAVA_{level}$ because when it is too high, $NAVA_{level}$ can cause irregular breathing pattern [20]. NAVA requires a nasogastric tube, this feeding tube can be contraindicated. Lastly a poor quality of EAdi signal might affect NAVA use.

7.7 Conclusion

NAVA and EAdi monitoring can improve patient's ventilator interaction and allow a more personalized care, which takes into account the patient's respiratory drive. NAVA can improve the match between the patient and the ventilator and provide the potential for both lung and diaphragm-protective ventilation. Some data suggest that NAVA, with an appropriate method of titration based on the individual neural feedback, might reduce the duration of mechanical ventilation.

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Proportional Assist Ventilation

8

Eumorfia Kondili and Evangelia Akoumianaki

8.1 Introduction

Proportional assist ventilation (PAV) is a mode of assisted ventilatory support introduced by Magdy Younes in 1992 [1]. With PAV, the ventilator delivers a pressure in the airway (Paw) that is always proportional to patient ventilation demands. The updated version of PAV, the PAV+ (proportional assist ventilation with adjustable gain factors), is currently available in the clinical practice. With PAV+, the software permits the semi-continuous measure of respiratory system mechanics and appropriately adjusts the ventilator parameters [2–4]. This chapter highlights the basic operation principles of PAV and PAV+, the evidence supporting this mode's effectiveness, and methods for titration of ventilation assistance.

8.2 Operation Principles

With PAV, the ventilator, once triggered, provides a pressure (Paw) which is always proportional to instantaneous inspiratory flow (V') and volume (V) and thus to the patient's inspiratory muscle pressure (Pmus) [1]. The ventilator monitors (V') and (V) and generates pressure which is, at any time during inspiration, the sum of the instantaneous V' and V and multiplied by a preset gain factor (% assist):

$$\text{Paw} = \%\text{assist}\left(V' \times \text{Rrs} + V_{\text{T}} \times \text{Ers}\right)$$

where Rrs and Ers are the resistance and elastance of the respiratory system, respectively.

E. Kondili (✉) · E. Akoumianaki
Department of Intensive Care Medicine, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece
e-mail: kondylie@uoc.gr

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The clinician sets the gain expressed as a percentage of Rrs and Ers (maximum 95%). The set %gain of assist reduces the pressure that the inspiratory muscles (Pmus) have to generate. Therefore, with PAV, the ventilator amplifies patient inspiratory effort without imposing any target either for flow, volume or Paw.

The proper function of PAV necessitates both regular and accurate assessment of respiratory system mechanics, which is difficult and time-consuming in assisted ventilation, so that the widespread use of PAV in clinical practice was significantly limited.

The updated version of PAV, PAV+ has an incorporated software that permits the non-invasive calculation of the respiratory system mechanics semi-continuously and automatically adjusts the flow and volume assist as always to represent constant fractions of the estimated values of Rrs and Ers [2–5].

The calculation of Rrs and Ers is based on the specific feature of PAV: the tight connection between the mechanical and neural breath [2–4]. Hence, at the end of mechanical inflation, Pmus is assumed to be in the declining phase (or it is already zero). Applying an airway occlusion at this point, Paw represents the elastic recoil at the corresponding volume (V_T) [3]. Based on this principle, calculation of respiratory system mechanics in PAV+ is performed automatically by the ventilator by applying at random intervals of 4–7 breaths, a 300 ms pause maneuver at the end-inspiration (Fig. 8.1a).

Airway pressure at the end of the occlusion ($Paw_{occlusion}$) is measured, and Ers and compliance (Crs = 1/Ers) are calculated as follows:

$$\text{Ers} = \left(\text{Paw}_{\text{occlusion}} - \text{PEEP}\right) / V_T$$

and

$$\text{Crs} = V_T / \left(\text{Paw}_{\text{occlusion}} - \text{PEEP}\right)$$

where PEEP is the positive end-expiratory pressure [3]. In the presence of intrinsic PEEP, the calculated value of Ers overestimates the respiratory system elastance, and the calculated Crs underestimates respiratory system compliance.

The measurement of Rrs is performed during the expiration following the pause maneuver (Fig. 8.1b). Assuming that the expiratory flow early in exhalation is driven by the elastic recoil pressure (i.e. alveolar pressure, Palv), the software identifies three points on the expiratory flow-time waveform corresponding to peak flow and 5 ms and 10 ms later. At these points, Palv and total expiratory resistance (R_{TOT}) are calculated as follows:

$$\text{Palv} = \text{Paw}_{\text{occlusion}} - \Delta V \times \text{Ers}$$

and

$$R_{TOT} = \left(\text{Palv} - \text{Paw}\right) / V'$$

where ΔV is the exhaled volume up to the point of interest and V' and Paw are the corresponding expiratory flow and airway pressure, respectively [4].

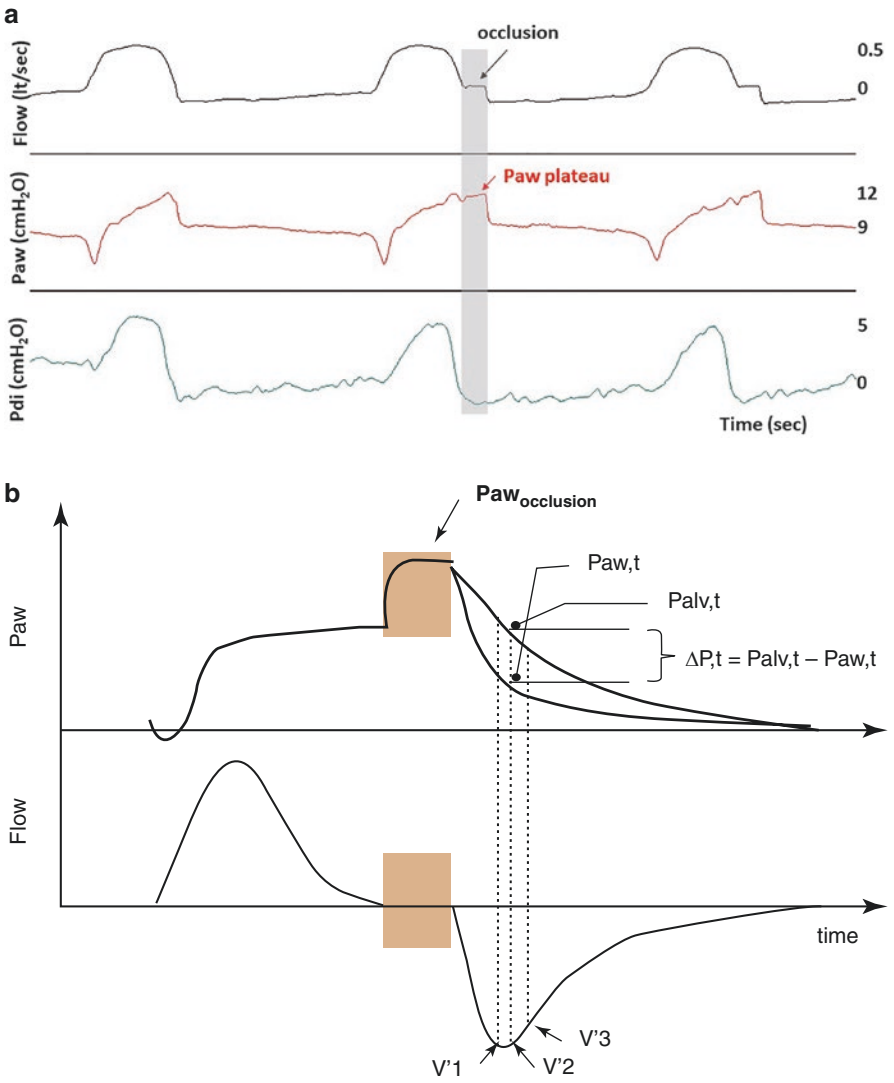

Fig. 8.1 (**a**) Flow, Airway Pressure (Paw), and transdiaphragmatic pressure (Pdi-time waveforms in a patient ventilated with PAV+). Observe an end-inspiratory pause maneuver during the second breath (shaded area). The maneuver is performed near the end of the neural breath when (Pdi) declines to zero and, therefore, there is no patient effort. Paw measured at the end of the maneuver is the $Paw_{occlusion}$ pressure (representing the elastic recoil pressure) used to calculate respiratory system elastance. (**b**) Estimation of respiratory system resistance: The shaded area represents the time of the end-inspiratory pause maneuver, which is followed by the exhalation in which respiratory resistance is calculated. The arrows indicate the three time points at which the resistance is calculated: the point of maximum expiratory flow ($V'1$) and after 5 ms ($V'2$) and 10 ms ($V'3$). At these points, the ventilator measures the airway pressure (Paw, t), the expiratory volume (ΔV_T, t), and the flow (V'). Elastance (ErsPAV) has been previously calculated during end-inspiratory occlusion. The alveolar pressure (Palv,t) at each time point is given by the equation $Palv,t = Paw_{occlusion} - \Delta V_T$, t × ErsPAV. The difference of Palv,t − Paw,t divided by the flow (V') gives R_{TOT} at each point in time

The values of R_{TOT} at these points are averaged to obtain the estimated R_{TOT}, which is the sum of the flow-dependent resistance of the endotracheal or tracheostomy tube (Rtube) and that of the respiratory system (Rrs_{PAV}). Rtube is calculated using the following equation:

$$\text{Rtube} = a + bV'$$

where a and b are constants, depending on tube length and diameter, respectively, estimated in vitro. Rrs_{PAV} is derived by subtraction of Rtube from R_{TOT} [4].

It is important at the start of ventilation on PAV+ the physician to correctly set both the type (endotracheal tube or tracheostomy) and the diameter of the tube. Otherwise, estimation of R_{TOT} will be inaccurate, which may lead to either under- or over-ventilation assist.

It should be noticed that this method measures expiratory resistance, while PAV+ calculation is based on inspiratory resistance (assuming a negligible difference between the two). However, if the difference between inspiratory and expiratory resistance is high (i.e., as in obstructive lung disease), the calculated Rrs is inaccurate, resulting in an adequate assist level. Furthermore, in the presence of PEEPi, the calculated value of R_{TOT} underestimates the actual value.

8.3 Advantages of PAV+

The cardinal difference between PAV+ and conventional assisted modes (pressure support ventilation, PSV; assist volume control, AVC) is that the ventilator assist is driven by patient's inspiratory effort [1, 2]. This feature, along with the improved matching of mechanical and neural inspiratory time, has beneficial effects in assistance optimization, patient–ventilator synchrony, and breathing pattern.

8.3.1 Protection from Over- or Under-Assistance

During assisted mechanical ventilation setting, ventilation assistance aims at avoiding under- or over-assistance-related complications. During AVC, a fixed V_T, unrelated to Pmus is delivered. In PSV, a preset pressure supports the Pmus, causing a parallel upward shift of the unassisted Pmus-V_T relationship. In both modes, a minimum V_T is delivered once the ventilator is triggered, depending on respiratory mechanics and level of assistance. Herein lies the major advantage of PAV+: the delivered V_T is proportional to inspiratory Pmus as changes in % assist alter the slope of unassisted Pmus − V_T relationship (Fig. 8.2). No V_T is delivered if there is no Pmus. When assistance is high, the activation of negative feedback mechanisms (Hering–Breuer reflex, vagally controlled reflexes) and unfavorable diaphragmatic length-tension properties will reduce V_T, protecting the lungs and diaphragm from over-assistance [2]. Indeed, studies have shown that in the majority of patients ventilated with PAV, inspiratory plateau and driving pressures were maintained within "safe" limits [6, 7]. Because assistance in PAV follows changes in respiratory

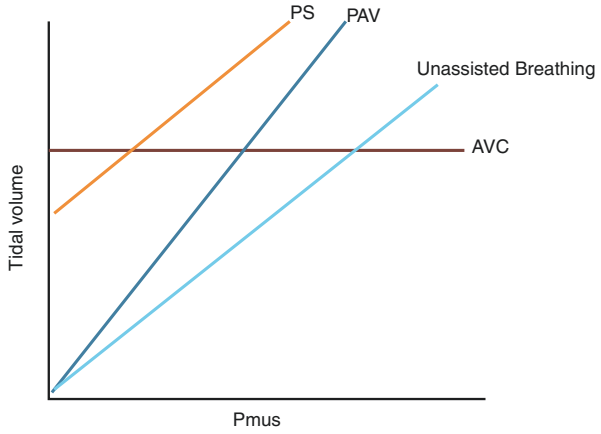

Fig. 8.2 Schematic presentation of the relationship between patient's inspiratory effort (muscle pressure, Pmus) and tidal volume (V_T) during an unassisted breath (light blue line), ventilation with PS (orange line), AVC (brown line), and PAV+ (blue line). During unassisted breathing, the increases in Pmus result in a relatively linear increase in V_T. With AVC, a pre-set V_T is delivered independent of the patient's effort, and the slope of the $Pmus_{peak}$–V_T relationship is always zero. During PS, a pre-set pressure is applied to the respiratory system after triggering, regardless of $Pmus_{peak}$, resulting in a parallel upward shift of the unassisted Pmus−V_T. With PAV+ the delivered V_T is proportional to inspiratory Pmus as changes in % assist alter the slope of the unassisted Pmus−V_T relationship. Observe that with PS and AVC, but not with PAV+, V_T may be substantial even at very low $Pmus_{peak}$

demands, it is associated with a lower increase in respiratory muscles effort and oxygen consumption during exercise or respiratory system mechanics increase compared to PSV [5, 8].

8.3.2 Breathing Pattern and Patient–Ventilator Interaction

Unlike conventional assisted modes in where V_T variability is either completely lost (AVC) or significantly suppressed (PS), with PAV, patients preserve their normal breathing pattern variability over a wide range of assist [5, 9, 10]. The breathing pattern in PAV is more influenced by the ventilator demands of the patient than assist level [5, 9, 10].

Patient–ventilator dyssynchrony—commonly present during conventional assisted modes—may harm the lung and the diaphragm, increase the work of breathing, cause or worsen dynamic hyperinflation, and eventually affect patients outcomes [11]. Several studies have demonstrated that PAV notably improves patient–ventilator interaction and decreases the incidence of ineffective efforts, expiratory triggering delay, and other major asynchronies [5, 6, 9, 10, 12] primarily because it prevents over-assistance and, secondarily, through amelioration of expiratory asynchronies.

8.3.3 Clinical Outcomes

A randomized study comparing PS with PAV+ tested whether these advantages of PAV+ translate into improved patient outcomes [6]. The proportion of patients who failed during assisted MV and were switched to control MV was two times higher in the PS group. A recent meta-analysis demonstrated that, compared to PS, PAV was associated with a reduction in weaning failure and reduced duration of MV [12]. So far, no difference in ICU- and in-hospital mortality or length of ICU stay has been evidenced with PAV+ compared to PS [6, 12].

8.4 Limitations in PAV/PAV+ Use

PAV/PAV+ may lead to inappropriate ventilator assist and should be applied with caution in the following conditions:

- In patients with low respiratory drive; as inspiratory efforts drive the ventilator there is a risk of hypoventilation.
- Dynamic Hyperinflation; Part of inspiratory effort (equal to that dissipated for ventilator triggering) is not assisted [5].
- Overestimation of Ers and Rrs: Based on PAV operation principles, there is a risk of over-assistance (excessive pressure or volume delivery) a phenomenon described as "runaway". Runaway occurs when the flow and volume assist are set to values greater than the actual Rrs and Ers values, respectively. As a result the pressure provided by the ventilator during the inflation may exceed the sum of elastic and resistive pressures, and the ventilator continues to deliver volume beyond the end of the inspiratory effort. It should be noticed that runway was a concern with PAV, but it rarely occurs with PAV+ and only when the gain approaches 90%.
- In the presence of excessive inspiratory leak; similar to respiratory system mechanics overestimation (see above), inspiratory leaks (i.e, non-invasive application of PAV, circuit leaks, bronchopleural fistula), may be associated with a runaway. The ventilator misinterprets the flow leak as a continuous patient effort and extends the assist delivery after the termination of the patient's inspiratory effort.

8.5 Titration of Assistance in PAV+

Despite its advantages, the diffusion of PAV+ in clinical practice is limited, mostly due to unfamiliarity with the titration of gain. Carteaux et al., proposed to adapt PAV+ gain according to an estimated inspiratory muscle effort ($Pmus_{Peak}$) [13]. As

PAV+ delivers Paw, which is proportional to Pmus, the latter is estimated using the following equation:

$$\text{Pmus}_{\text{peak}} = \left(\text{Paw}_{\text{peak}} - \text{PEEP}\right) * \left(\left(100 - \%\text{assist}\right) / \%\text{assist}\right)$$

The %gain should target a Pmus value between 5 and 10 cmH_2O, corresponding to Pmus pressure–time product between 50 and 150 cmH_2O s min^{-1}. Although feasible, the accuracy of estimated $Pmus_{peak}$ to predict actual inspiratory muscle effort is questionable and might result in over- or under-assistance in almost 50% of patients [14]. Moreover, $Pmus_{peak}$ is underestimated in patients with PEEPi [14, 15].

An alternative clinical approach is to initiate PAV+ at high gain levels (i.e., 70–80%) and then decrease % gain stepwise, by 5–10%, to the lowest level not associated with hypercapnia or signs of respiratory distress. Regarding PEEP, compliance measurement with PAV+ can be used to indicate the optimal PEEP; alveolar recruitment after an increase in PEEP will improve compliance. Furthermore, the driving pressure of the respiratory system can be continuously calculated as the ratio between V_T and Crs (taking advantage of the measurement during short occlusion) to estimate the risk of lung injury. If the DP remains high despite PEEP and assistance optimization (i.e, severe ARDS and/or high respiratory drive), sedation and controlled MV might be necessary.

8.6 Conclusion

PAV/PAV+ is a proportional mode of assisted mechanical ventilation, in which the ventilator provides pressure which is always proportional to instantaneous flow and volume, and thus to the patient's ventilator demands. Clinical studies have demonstrated that ventilation on PAV/PAV+ compared to conventional modes of assisted mechanical ventilation is associated with better patient–ventilator asynchrony, lower risk of under- or over-ventilator assistance, and decreased rate of weaning failure.

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Non-Invasive Ventilation: Indications and Caveats

9

Oriol Roca, Domenico Luca Grieco, and Laveena Munshi

9.1 Introduction

In the last few decades, indications for non-invasive ventilation (NIV) in patients with acute respiratory failure have expanded considerably [1]. Compared to invasive mechanical ventilation, NIV is simpler to use and, with appropriate expertise and monitoring, it may even be applied outside intensive care units (e.g. emergency room, high-dependency units). However, it should be noted that these devices primarily act to support the patient through their respiratory failure while waiting for the underlying pharmacologic treatment to take effect. NIV can be applied using different interfaces and modes of ventilation resulting in different physiological effects.

O. Roca (✉)
Servei de Medicina Intensiva, Hospital Universitari Vall d'Hebron, Institut de Recerca Vall d'Hebron, Barcelona, Spain

Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CibeRes), Madrid, Spain
e-mail: oroca@vhebron.net

D. L. Grieco
Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, Fondazione 'Policlinico Universitario A. Gemelli' IRCCS, Rome, Italy

L. Munshi
Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

Department of Medicine, Sinai Health System and University Health Network, Toronto, ON, Canada
e-mail: laveena.munshi@sinaihealth.ca

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9.2 NIV Interfaces

NIV can be delivered through different interfaces (Fig. 9.1). The most common interface to deliver NIV is a face mask (oronasal or full-face). The main differences between oronasal and full-face masks are their internal dead space and their ability

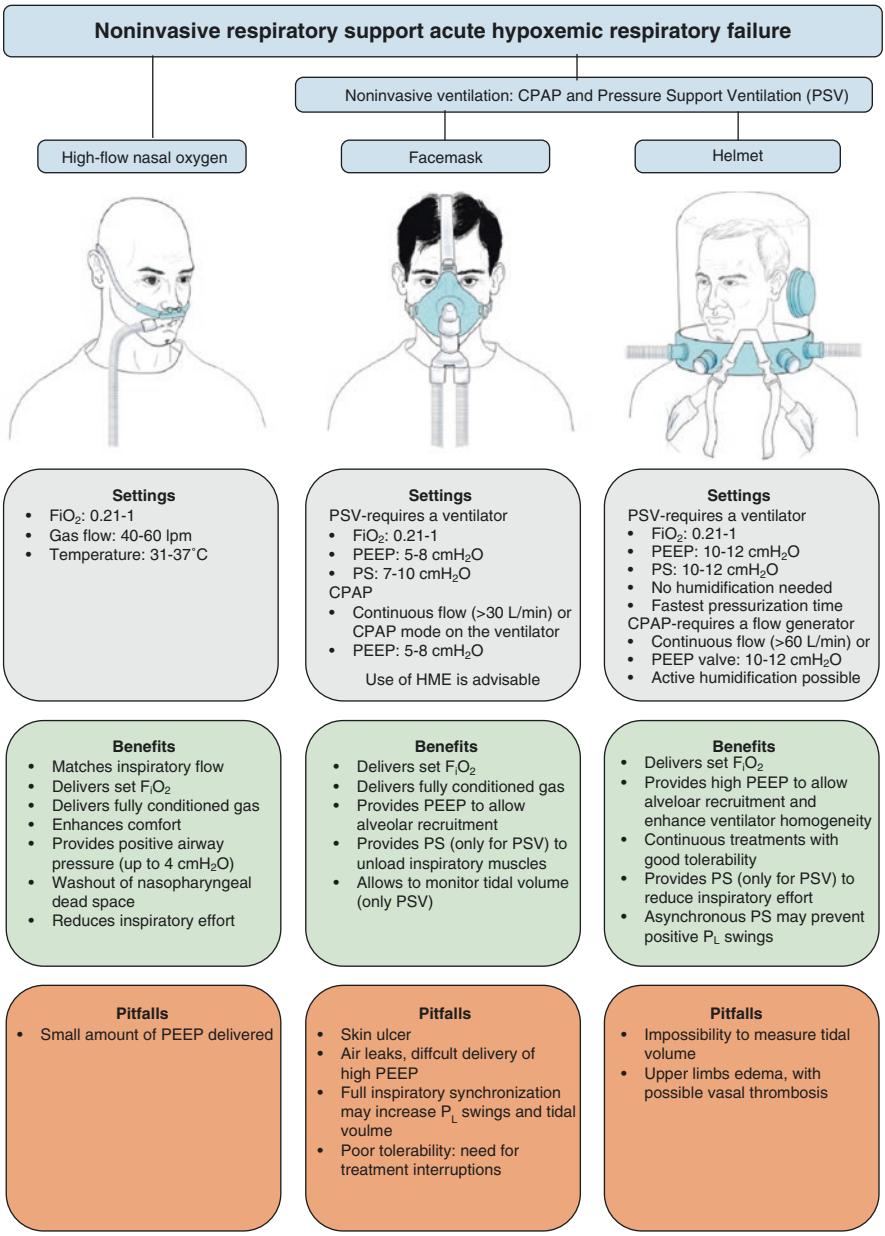

Fig. 9.1 Modes and interfaces of noninvasive respiratory support

to effectively delivery positive end-expiratory pressure (PEEP). The difference across the interfaces, however, does not lead to significant dead space effect on arterial carbon dioxide levels, minute ventilation, or patient's effort [2]. Similarly, it has been shown that effective dead space across these two interfaces is not related to the internal gas volume included in the interfaces. The results of these studies suggest that the oronasal and full-face-mask interfaces may be interchangeable when considering dead space and carbon dioxide. The full-face mask may have advantages over the oronasal interface given its ability to deliver PEEP more effectively given the seal that can be generated.

Another increasingly popular interface in the critical care setting is the helmet, which is a clear transparent hood that covers the entire head of the patient. Helmet has a soft collar seal at the neck. The potential benefit of helmet over the face-mask interface is an even greater seal allowing for enhanced delivery of PEEP without substantial leak. Moreover, it may be better tolerated allowing to substantially increase the duration of the NIV therapy. Importantly, high fresh gas flows are required (typically above 40 L/min) to minimize the risk of carbon dioxide rebreathing [3].

9.3 Mode of Ventilation

In clinical practice, NIV is primarily delivered as a means of bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). BiPAP, also referred to as pressure support ventilation (NIV-PS), is characterized by the use of two levels of pressure: pressure support and PEEP. Unlike BiPAP, CPAP does not provide any inspiratory support [4]. Although ICU ventilators can administer CPAP-NIV, in order to adequately fulfill patients' flow needs and maintain a set pressure over the whole respiratory cycle, the use of oxygen/air blenders or venturi systems continuously delivering high flows are necessary during Helmet CPAP. They should also be encouraged also when oronasal and full-face mask are the chosen interfaces.

The use of proportional ventilatory modes (i.e. proportional assist ventilation and neurally adjusted ventilatory assist) is also under evaluation to optimize patient–ventilator interaction and tolerance during NIV [5, 6]. These modes are not widely used in clinical practice.

9.4 Physiological Effects of NIV

The physiological benefits of NIV supportive therapies in ARF are well described [7]. Both CPAP and BiPAP may increase end expiratory lung volume through lung recruitment (thereby reducing intrapulmonary shunt and potentially dynamic strain) [8], and improve cardiac function in case of concomitant heart failure by reducing left ventricular afterload and right ventricular preload (see also Chap. 19) [9]. These changes can lead to improved arterial oxygenation. It is worth noting that CPAP and BiPAP have distinct physiologic effects. Despite both techniques improve oxygenation, the application of CPAP only does not result in a reduction in inspiratory

effort compared to BiPAP [8]. This may partially explain why CPAP has only been associated with transient improvements in oxygenation and dyspnea with no effects on intubation rates in a mixed population of patients with acute hypoxemic respiratory failure (AHRF) of different etiologies [10].

The unique physiologic properties of BiPAP and CPAP make them useful as a supportive care modality across different etiologies of acute respiratory failure. Patients with acute exacerbation of chronic obstructive pulmonary disease experience hypercapnic respiratory failure through an inability of the respiratory system to achieve sufficient alveolar ventilation through bronchoconstriction and eventual respiratory muscle fatigue. BiPAP facilitates tidal volume support, resulting in larger tidal volumes, less respiratory muscle fatigue resulting in better carbon dioxide clearance and lower work of breathing. This strategy can support the patient while targeted therapies to address inflammation and bronchoconstriction, and the underlying cause, take effect.

CPAP-NIV can ameliorate both cardiovascular and respiratory physiology in the setting of hydrostatic pulmonary edema inducing acute, severe respiratory failure. By increasing the intrathoracic pressure left ventricular afterload and right and left ventricular preload can be reduced. Furthermore, in severe acute respiratory failure with respiratory distress, hypoxia and hypercapnia, the addition of supportive tidal volumes with inspiratory positive airway pressure can help minimize work of breathing while the underlying congestive heart failure pharmacologic treatment takes effect.

In patients with de-novo AHRF, the application of CPAP/PEEP through NIV may facilitate the opening of distal airway and alveoli resulting in lung recruitment, decreased shunt, improved respiratory mechanics, and functional residual capacity. Finally, in the presence of muscle fatigue, the addition of inspiratory support by using BiPAP mode may decrease the work of breathing, that could be also partially alleviated by the recruitment induced with CPAP application.

9.5 Indications for NIV

Recommendations of current guidelines for the use of NIV in different clinical scenarios are summarized in Fig. 9.2.

9.5.1 Hydrostatic Pulmonary Edema

The use of NIV, and in particular CPAP, has been studied extensively in the setting of cardiogenic pulmonary edema. In the absence of acute shock or acute need for revascularization therapy, NIV, in addition to pharmacologic interventions, is recommended as first line supportive therapy for patients with cardiogenic pulmonary edema according to numerous clinical practice guidelines [11].

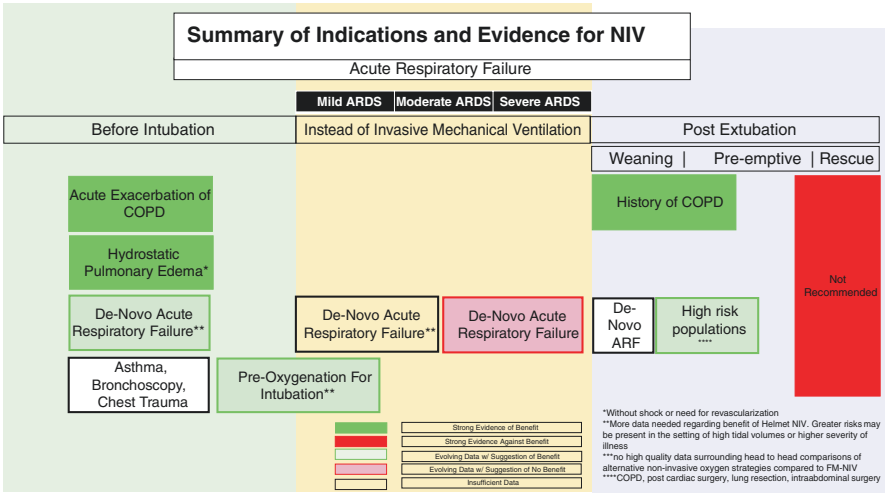

Fig. 9.2 Recommendations of current guidelines for the use of NIV in different clinical scenarios

9.5.2 Hypercapnic Respiratory Failure: Acute Exacerbation of COPD

There have been numerous randomized controlled trials demonstrating the benefit of face-mask NIV (specifically BiPAP) above standard oxygen therapy in severe acute exacerbation of COPD. Multiple consensus conferences and clinical practice guidelines make a strong recommendation for its use given the high levels of success in preventing intubation and decreasing mortality across the evidence available [11, 12].

9.5.3 De-Novo Acute Hypoxemic Respiratory Failure

9.5.3.1 Facemask NIV

Data supporting the use of prophylactic face-mask NIV to prevent intubation compared to alternative non-invasive strategies have been conflicting with some studies suggesting benefit [13], some studies suggestion no difference [14], and others suggesting possible harm [15]. In a recent network meta-analysis comparing all non-invasive oxygen modalities, there was a significantly lower odds of endotracheal intubation with face-mask NIV (RR, 0.76, 95%CI 0.62–0.90) and death (RR, 0.83, 95%CI 0.68–0.99) compared to conventional oxygen therapy [16]. This data suggests that there may be a role of face-mask NIV in preventing intubation or early AHRF management. However, the application of face-mask NIV may not be without risk. Indeed, NIV failure is particularly concerning given the higher mortality

compared to NIV success or early initiation of invasive mechanical ventilation [17]. Moreover, in the network meta-analysis conducted, the mortality benefit associated with face-mask NIV was no longer present across higher severities of acute respiratory failure [16].

9.5.3.2 Helmet NIV

Emerging data has demonstrated the potential benefit of helmet NIV compared to facemask NIV in patients with AHRF [18]. In the network meta-analysis comparing all non-invasive modalities, helmet NIV was associated with a decreased risk of intubation (RR, 0.26 (95%CI 0.14–0.45)) and decreased mortality (RR, 0.40 (95%CI 0.24–0.63)) compared to conventional oxygen therapy [15]. The mortality and intubation benefits were also seen compared to other modalities (high-flow nasal oxygen and face-mask NIV) but this was based upon a small number of studies. Furthermore, emerging data from the COVID-19 pandemic has suggested a decreased risk of intubation with the application of helmet NIV compared to high-flow nasal cannula (see chapter on non-invasive oxygen strategies during COVID-19) [19].

9.5.4 Immunocompromised Patients

Immunocompromised patients represent a special population of patients with AHRF. It has been shown the ability of facemask NIV to prevent intubation and death across immunocompromised patients compared to standard oxygen therapy [20]. However, much has changed in the infectious disease and supportive care approach to critically ill immunocompromised patients with lower mortality rates in the face of invasive mechanical ventilation. In fact, in the network meta-analysis, the direction of effective was similar in the immunocompromised patient population compared to the non-immunocompromised studies [16]; therefore, contemporary data does not support a different strategy in this population.

9.5.5 Pre-Oxygenation

Some early data suggested potential benefit of facemask NIV as the pre-oxygenation strategy before endotracheal intubation compared to bag-mask ventilation [21]. It may decrease the frequency and the degree of desaturations during intubation. Interestingly, given the added benefit of continued application of the high-flow nasal cannula, the combination of NIV added to HFNC has been evaluated during the intubation procedure in AHRF reducing the oxygen desaturation during the intubation [22].

9.5.6 After Invasive Mechanical Ventilation

9.5.6.1 Early Liberation

The application of NIV as a weaning strategy has been evaluated across a series of studies. This strategy, in select patients (particular those with COPD), has been found to reduce time with an endotracheal tube [23]. However, these studies have not consistently translated to improvements in ICU length of stay or mortality [24].

9.5.6.2 Pre-Emptive Strategy

Approximately 10–20% of patients who fulfill weaning criteria and spontaneous breathing trial will fail extubation. Face-mask NIV has been evaluated as a strategy to prevent this across those at high risk for extubation failure. This strategy has been particularly useful for patients with COPD, elderly patients, those with cardiac or respiratory co-morbidities. Several studies have evaluated the pre-emptive application of NIV post-operatively in specific populations (post-cardiac surgery, abdominal surgery, lung resection) with lower rates of intubation compared to standard oxygen therapy [25].

9.5.6.3 Post-Extubation Acute Respiratory Failure Rescue

The application of NIV as a rescue maneuver to "prevent" reintubation has not been shown to be beneficial (outside, perhaps, overt flash pulmonary edema). Furthermore, it has been shown to delay reintubation and increase mortality [26]. The rationale for this is likely due to the fact that extubation failure may be due to the underlying disease or accumulated respiratory muscle weakness that may not be reversible with transient NIV.

9.5.7 Insufficient Data

Insufficient high-quality data exists surrounding the application of NIV in the setting of asthma exacerbations, chest trauma, and peri-bronchoscopy.

9.6 The Importance of Monitoring of Patient with NIV

9.6.1 Monitoring the Patient with NIV

The use of any kind of NIV respiratory supportive therapy can mask signs of respiratory deterioration, delaying time to intubation. Delayed intubation may lead significant patient self-inflicted lung injury (P-SILI), peri-intubation hypoxemia, and potentially worse outcomes [27]. Given the potential for rapid deterioration and the need for sufficient expertise to identify when this is occurring, close patient

monitoring is essential when using NIV. Expertise in titration of the device, recognition of ineffective ventilation, identification of injurious tidal volumes or impending respiratory fatigue are necessary to evaluate when transition to intubation must occur.

Patient self-inflicted lung injury is a recently described phenomenon where spontaneous breathing may exacerbate lung injury. P-SILI is thought to arise from spontaneous efforts made by a patient with damaged lungs and a high respiratory drive. It is believed that the vigorous inspiratory efforts can produce high transpulmonary pressure swings which may result in global/regional pressure/volume changes, which may further aggravate the existing lung injury [28]. The same profoundly negative deflection in pleural pressure increases vascular transmural pressure and vessels permeability, contributing to alveolar floating [29]. In addition, with insufficient PEEP, which may be seen during facemask NIV or HFNC (2–7 cmH_2O), the patient may be susceptible to atelectrauma—injury due to cyclical alveolar opening and closing. Finally, an intra-tidal shift of gas from nondependent to dependent lung regions due to different transmission in lung tissue of diaphragm contraction has been recently identified in the very early phase of inspiration of spontaneously breathing patients with ARDS [30]. This pendelluft phenomenon results in overstretching of the dependent lung regions, independently from the size of the inspired tidal volume. This has been recently shown to exacerbate lung injury during spontaneous breathing. This phenomenon may be seen in any spontaneously breathing patient—including those under NIV. Optimal mechanisms of identifying when spontaneous breathing may be harmful and when to escalate to invasive mechanical ventilation (and sedation/paralysis to remove spontaneous efforts) are not yet clearly defined.

9.6.1.1 Predicting NIV Failure in the Setting of De-Novo AHRF

Moderate to severe hypoxia (PaO_2/F_IO_2 < 150 mmHg) has been repeatedly associated with a higher risk of NIV failure and worse outcomes in patients with de-novo AHRF [1, 31]. More recently, a clinical scale to predict NIV failure has also been developed [27]. It is calculated by using variables that can be easily measured at the bedside including Heart rate, Acidosis, level of Consciousness, Oxygenation (PaO_2/F_IO_2), and Respiratory rate (HACOR score) (Table 9.1). This scoring system allows dynamic monitoring of the risk of intubation during NIV. Patients with a HACOR score > 5 are at higher risk of NIV failure.

The lack of reduction of inspiratory effort after the initiation of NIV has been associated with NIV failure and increased mortality. High inspiratory effort may generate large tidal volumes and lead to the development of P-SILI as highlighted above [31, 32]. Given this, tidal volumes <9 mL/kg of predicted body weight should be evaluated early in the application of face-mask NIV. It should be noted that exhaled tidal volumes are not reliably measured with the Helmet interface. Similarly, change in inspiratory effort (ΔPes <10 cmH_2O) could be also monitored. Finally, a recent physiological study showed that a diaphragmatic thickening fraction (DTF) < 36% and a respiratory rate/DTF ratio < 0.6 are predictors of NIV outcome [33].

Table 9.1 HACOR score for prediction of NIV failure [27]

Variables	Category	Points
Heart rate (beats/min)	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
GCS	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/F_IO_2	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate (breaths/min)	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

9.6.1.2 Predicting NIV Failure in the Setting of Hypercapnic ARF

Pathophysiological mechanisms associated with NIV failure in hypercapnic patients may be different. In these patients, arterial blood pH and the change in $PaCO_2$ have been associated with NIV failure [34]. The HACOR score has also been evaluated in this population and may be a useful tool to identifying hypercapnic patients at higher risk of failure [35]. Finally, the presence of ineffective efforts due to the presence of intrinsic PEEP or muscle weakness, as well as the presence of asynchronies may be also predictors of failure.

9.7 Conclusions

BiPAP and CPAP have different physiological benefits that may be useful in different clinical situations. The physiologic properties of these devices as a supportive care modality may decrease the need for intubation and mortality across certain patient populations, but close monitoring must be provided especially to avoid delayed intubation. Much work needs to be done to better understand different phenotypes of respiratory failure that may benefit from NIV or are more at risk of developing P-SILI and have differential responses to facemask NIV, HFNC or helmet. Future research needs to help define which patients may benefit the most from each non-invasive device and at what thresholds should physicians' transition to invasive mechanical ventilation.

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High Flow Nasal Oxygen: From Physiology to Clinical Practice

10

Sharon Einav and Marta Velia Antonini

10.1 Introduction

Administration of heated and humidified oxygen via a broad-diameter nasal cannula was originally devised to improve racehorse performance. The ingenuous adaptation of this method of oxygen administration for human use was first implemented in neonates. Previous practice with nasal continuous positive airway pressure (CPAP) in this population had already proven that by matching the diameter of the nasal cannula to the diameter of the neonatal nares, leakage could be controlled. Combined with the relatively high compliance of the neonatal chest wall, nasal administration of flows rather than pressures seems to provide similar respiratory support with a lower risk of barotrauma and damage to nasal structures [1, 2]. In fact, the precision of fit is such that current pediatric research is looking into adjustment of flow rates based on work of breathing [3]. It was also believed that high flows may trigger spontaneous breathing in this apnea-prone population but this assumption has yet to be proven.

Neonatal experience with high flow nasal oxygen (HFNO) was the paradigm shift that enabled translation of the use of this device from horses to humans. However, extrapolating neonatal and pediatric experience and research with this device to adult use is mistaken; both normal adult physiology and adult pathology differ greatly from those of neonates and children. The use of HFNO in critically

S. Einav (✉)
Surgical Intensive Care, Intensive Care Unit, Shaare Zedek Medical Center, Jerusalem, Israel

Anesthesiology and Intensive Care, Hebrew University Faculty of Medicine, Jerusalem, Israel
e-mail: einav_s@szmc.org.il

M. V. Antonini
Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

G. Bellani (ed.), *Mechanical Ventilation from Pathophysiology to Clinical Evidence*, https://doi.org/10.1007/978-3-030-93401-9_10

ill adults has become all pervasive due to the simplicity of these standalone devices [4]. This chapter will therefore focus on the physiological effects of the high flow nasal cannula in adults and their implications for treatment as well as future research.

10.2 Dead Space, Air Entrainment, and Washout

In healthy adults the anatomical dead space equates the physiological dead space and normally approximates 2 ml/kg of body weight. A normal adult therefore rebreathes approximately one-third of each tidal volume. Pathological processes may significantly increase the physiological dead space and such changes have been proposed to correlate with mortality. When the anatomical dead space increases, reducing the amount of physiological dead space by eliminating rebreathing may be crucial.

Flushing of the airway with gas containing a high percentage of oxygen before initiation of inspiration has long been used for increasing the fraction of inspired oxygen (FiO_2). The main limitation to this method was an inability to match high inspired flow rates, which may exceed 50 L/min in dyspneic patients [5], not in the least because such flows cause severe discomfort with an open gas circuit [6]. If the peak inspiratory flow rate of the patient is not matched by the set flow, environmental air will be entrained, decreasing the FiO_2 during inspiration.

High flow nasal oxygen administration systems maintain gas humidity despite flow rates up to 60 L/min [7]. Laboratory studies [8], studies conducted on human volunteers [9] and studies in patients with airway disease [10, 11] show that humidification improves mucociliary clearance of airway secretion and prevents the increase in airway resistance induced by cold gas flows. Some devices also allow adjustment of the temperature of the inspired flow to patient preferences, which may increase tolerance [12] (Table 10.1).

Administration of oxygen through high flow nasal systems also provides a stable FiO_2. The use of flow rates that exceed those required by the patient prevents air entrainment and supplants expired air with fresh gas in the upper anatomical dead space. The washout effect of high oxygen flow has been described in both simulation models and human studies and is probably more effective with an open mouth [13, 14].

Table 10.1 The characteristics of standalone HFNO devices

Device	Flow rate (L/min)	Relative humidity (%)	Gas temperature °C (°F)
Vapotherm	5–40	95–100	33-–43 (91.4–109.4)
Optiflow	1–60	100	37 (98.6)
Airvo	2–60 (adult configuration) 2–25 (junior configuration)	95 (between 10 °C and 30 °C)	37 (98.6), 34 (93), 31 (88)

10.2.1 The Way Forward

Several ventilators that have been fitted with HFNO modules provide consistent flows and FiO_2 s comparable to those provided by standalone HFNO devices [15]. This opens the way to the possibility of providing HFNO combined with other modes of ventilation. Grofalo et al. recently described healthy volunteers treated with both helmet CPAP (5 and 10 cm H_2O) and HFNO (flows of 30, 40, and 50 L/min) at the same time. At no time was helmet fogging or discomfort an issue and that at all flows breathing frequency was slightly, but significantly, lower with combined CPAP and HFNO than with HFNC alone [16].

10.3 Generation of PEEP (or Not)

Studies describing generation of high positive end-expiratory pressures (PEEP) with HFNO in neonatal and pediatric populations abound. These have probably led to the misguided belief that this effect is identical in adult patients. In fact, the relation between HFNO and PEEP in adults seems somewhat more complex than that observed in children.

Early studies conducted in healthy adult volunteers and patients scheduled for elective cardiac surgery noted that hypopharyngeal pressures rose almost parallel to increasing delivered gas flow rate but barely exceeded 7–8 cm H_2O even at flows of 50 L/min with a closed mouth [17, 18]. Leaks seem to affect the initial pressure but not the pressure increment generated by an increased flow [18, 19]. As pressure is usually consistent across the airway, a rise in hypopharyngeal pressure reflects a certain degree of rise in alveolar pressures. The amount of PEEP generated depends mostly on the set flow rate but it is also related to peak inspiratory flow and tidal volume, both of which are determined by the patient and may change over time (Fig. 10.1).

10.3.1 The Way Forward

In patients after extubation, electrical impedance tomography (EIT) demonstrates that global end-expiratory lung impedance, regional recruitment, and overdistension increase parallel to an increase in HFNO flow rates. However, recruitment is greater in ventral than in dorsal lung regions and seems to depend on the proportion of baseline unrecruited areas [20]. Indeed, increasing set HFNO flow does not always create a predictable increase in end-expiratory lung volume, particularly in dependent lung zones [21].

So how can aeration be improved nonetheless? Administration of Nitrox and Heliox via a high flow nasal system to swine 4 h after oleic-acid induced lung injury improved ventilation efficiency and distribution (mainly with Heliox) and reduced the work of breathing (both Nitrox and Heliox) [22].

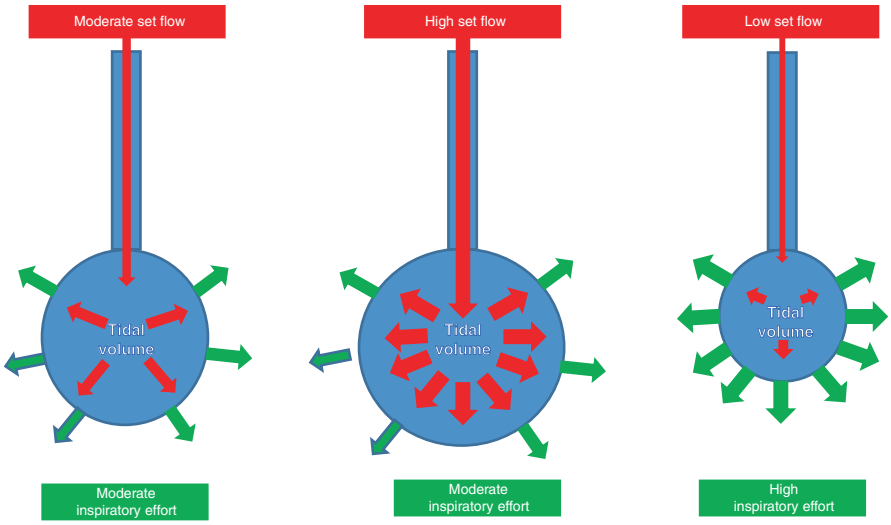

Fig. 10.1 Relationship between set flow, negative inspiratory effort, tidal volume, and positive end-expiratory pressure. Higher set flows and higher spontaneous tidal volumes increase the PEEP generated by HFNO while an increase in negative inspiratory effort decreases the PEEP generated by HFNO (concept created from data presented by Sun YH et al. Clin Respir J. 2019 Dec;13(12):758–764. doi: https://doi.org/10.1111/crj.13087. Epub 2019 Sep 8. PMID: 31465634 and Okuda M et al. BMJ Open Respir Res. 2017 July 20;4(1):e000200. doi: https://doi.org/10.1136/bmjresp-2017-000200. PMID: 29071075; PMCID: PMC5647476)

Alternatively, patients likely to benefit from HFNO may be identified a priori in the future. Lung recruitability, assessed by computed tomography as the amount of nonaerated tissue, seems associated with failure of HFNO but not of NIV treatment [23]. Individualized medicine in the context of HFNO may involve measurement of recruitability prior to initiation of treatment.

10.4 Work of Breathing (WOB)

Several studies suggest that the most important beneficial effect of HFNO may be a decrease in the WOB.

10.4.1 Work of Breathing in Normal Adults and in Hypoxemic Respiratory Failure

Takashima et al. used ultrasound measurements to study thickening fraction in adult critically ill patients with and without HFNO. Thickening fraction increased after withdrawal of HFNO in patients without diaphragm dysfunction but not in patients with decreased diaphragm contraction. HFNO also decreased paradoxical diaphragm contractions [24].

Studies of lung impedance also show decreased WOB with HFNO. Longhini et al. randomized patients undergoing flexible bronchoscopy to either HFNO or conventional oxygen via face mask. During the procedure patients with HFNO had more stable PaO_2 and less desaturations. End-expiratory lung volume (as measured by electrical impedance) and diaphragm shortening fraction remained unchanged with HFNO, whereas with conventional oxygen lung volume decreased and thickening fraction increased [25]. Pérez-Terán et al. studied lung impedance and diaphragmatic excursion by ultrasound before and after 30 min of respiratory support with non-invasive ventilation (NIV) or HFNO in healthy volunteers. Respiratory rate decreased and end-expiratory lung impedance increased in both groups, but the variation in end-expiratory lung impedance was higher with NIV than with HFNO [26].

Vargas et al. treated patients admitted to the ICU for acute hypoxemic respiratory failure with alternating 20-min sessions of oxygen via a high-FiO_2 non-rebreathing face mask, HFNO and CPAP. Compared with the face mask, both HFNO and CPAP significantly reduced inspiratory effort (assessed by esophageal pressure) but CPAP produced a greater improvement in PaO_2/FiO_2 [27]. Mauri et al. used electrical impedance tomography to study patients with acute hypoxemic respiratory failure during application of COT and HFNO with a constant FiO_2. These authors also showed that increasing flow rates significantly decreased inspiratory effort, improved aeration (end-expiratory lung volume), and improved dynamic lung compliance (the ratio of tidal volume to esophageal pressure) [21].

10.4.2 Work of Breathing in Patients with Decompensated Chronic Obstructive Pulmonary Disease (COPD)

Currently, clinical practice guidelines do not recommend HFNO for patients with an acute exacerbation of COPD. However, some recent data suggests that this approach may require rethinking in the future. Di Mussi et al. studied patients with COPD that had undergone intubation for hypercapnic respiratory failure. Post-extubation, treatment was provided with preset periods of conventional oxygen alternating with HFNO. An improvement was observed in both neuroventilatory drive (assessed by a decrease in electrical diaphragmatic activity) and work of breathing (assessed by inspiratory trans-diaphragmatic pressure-time product). When conventional oxygen therapy was changed to HFNO, an improvement was observed in both neuroventilatory drive (assessed by a decrease in electrical diaphragmatic activity) and work of breathing (assessed by inspiratory trans-diaphragmatic pressure-time product). This improvement was reversed when HFNO was changed back to conventional oxygen therapy. As FiO had been titrated to achieve a constant arterial O saturation target of 88–92% across all the study periods this change was attributed to the use of HFNO [28]. Studies of exercise performance with HFNO in patients with COPD also show significant decreases in CO_2 production, increases in exercise duration and less deoxygenated hemoglobin in muscle tissue [29, 30]. Extrapolation of these findings

to COPD exacerbations suggests that provision of HFNO may increase patient endurance and decrease the likelihood of fatigue and intubation.

10.4.3 The Way Forward

A recent study compared the mean inspiratory flow generated by intubated patients during a spontaneous breathing trial to the post-extubation HFNO set flow described as most comfortable by the patient after extubation (after testing 20 L/min to 60 L/min in 10 L/min increments). The FiO_2 was titrated to maintain SaO_2 92–97%. Pre-extubation mean inspiratory flow correlated with the HFNO set flows with which the patients were most comfortable [31]. The importance of this finding may extend well beyond patient comfort. Real-time monitoring of WOB with automated adjustment of flow may be the way forward to improving breathing synchrony and maintaining oxygen stability during HFNO treatment [3]. Non-invasive assessment of the WOB during treatment with HFNO has hitherto been confounded by the unidirectional flow of gas toward the patient. However, Montecchia et al. recently described the use of two pneumotachographs, combined with a leak correction algorithm. Measurements from a lung model and two healthy adult volunteers showed that that this method provided reliable estimates of respiratory flow and volume (needed for calculating WOB) with a relative error <1% [32].

10.5 Some Words of Caution

Three major safety concerns exist regards to administration of HFNO: Lack of device alarms, fatigue during treatment, and patient self-inflicted lung injury (PSILI).

Lack of device alarms may not seem a major issue in patients who are not sedated and are capable of speech. However, fatigue has been highlighted as a major concern in several studies showing increased mortality with the use of non-invasive respiratory support in the intensive care unit, even when using devices with alarms. Frizola et al. studied a swine model and noted that tracheal pressures increased in a flow-dependent manner and the increase was greater when similar flows were administered via two nares versus one [19]. While this observation may seem trivial, it instantly brings to mind the clinical implication of partial cannula dislodgement by a restless or drowsy patient. Indeed, accidental cannula compression or blockage have been described [15]. Moreover, patients may fall asleep during treatment and/or may not be capable of generating sufficient airflow to call for help. Regardless of the HFNO device being used, hypoxemic patients should always placed in a highly monitored environment.

Finally, PSILI is recognized as an important issue with the use of HFNO in the neonatal population. Resultantly, concerns have been raised regarding the inability

to monitor either pressures or volumes while using HFNO in other populations prone to PSILI [14].

10.6 Conclusion

Use of HFNO became pervasive due to the simplicity and efficacy of these stand-alone devices. HFNO systems provide several obvious physiological advantages. These include washout of airway dead space with oxygenated gas and minimization of rebreathing, maintenance of humidity despite the high flows, temperature adjustment to comfort levels, and provision of a stable FiO_2 in conditions of changing inspiratory flow rates. The amount of PEEP generated in adults is relatively low and depends not only on the set flow but also on patient-related variables (mouth closure, peak inspiratory flows, tidal volume, and lung compliance). The main benefit of HFNO seems mainly to be related to decreased work of breathing and reduction of fatigue. The effect of HFNO on aeration requires further elucidation as it most likely also depends on factors other than set flow. Although the guidelines do not recommend HFNO for patients with an acute exacerbation of COPD, there is early data suggesting that use of HFNO may unload inspiratory muscles at the beginning of inspiration in these patients, thereby increasing endurance. Looking forward, future developments may include provision of HFNO combined with other modes of ventilation, administration of gas mixtures such as Nitrox and Heliox via high flow devices, individualized assessment of lung recruitability and aeration patterns in order to select the appropriate patients for HFNO, and matching of device setting to patient inspiratory flows and work of breathing. Regardless of the indication for its use, HFNO should always be administered in a monitored environment to ensure patient safety.

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Nursing of Mechanically Ventilated and ECMO Patient

11

Marta Velia Antonini and Johannes Mellinghoff

Patients admitted to the Intensive Care Unit (ICU) for acute respiratory failure (ARF) or acute respiratory distress syndrome (ARDS) have complex clinical needs, starting with a demanding ventilatory management to provide oxygenation and CO2 removal, preventing additional injury to the lungs [1]. These critically ill patients are commonly unstable and may require additional interventions in spite of mechanical ventilation including prone positioning and extracorporeal life support [1]. To ensure compliance with these treatments they often require prolonged periods of deep sedation and possibly paralysis [1, 2], which impairs rehabilitation efforts and may lead to the development of psychological distress.

This short chapter aims to highlight the main peculiarities and challenges of nursing care in ICU patients requiring mechanical ventilation, prone positioning, and/or extracorporeal support.

M. V. Antonini (✉)
ECMO Team—AUSL della Romagna, Cesena, Italy

Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
e-mail: velian@unimore.it

J. Mellinghoff
University of Brighton, School of Sport and Health Sciences, Brighton, UK

G. Bellani (ed.), *Mechanical Ventilation from Pathophysiology to Clinical Evidence*, https://doi.org/10.1007/978-3-030-93401-9_11

11.1 Mechanical Ventilation

Nurses are crucial members of the multi-professional healthcare team and play a pivotal role in the implementation of evidence-based strategies such as the ABCDEF bundle [3, 4] which aims to liberate critically ill patients from iatrogenic consequences of treatments including pain, agitation/sedation, delirium, immobility, and sleep disruption. To maximize recovery, reduce ICU stay, and risk of post-intensive care syndrome (PICS, see also Chap. 26) these strategies are essential to minimize the long-term impact of critical care interventions and optimize cognitive and physical recovery [5].

Nurses are more specifically involved in the application of the following bundle elements:

- A and C: Assess, prevent, and manage pain, and choice of analgesia and sedation. These elements focus on the assessment and management of pain, including the choice of drugs for sedation and analgesia. Furthermore, tailoring these agents to sedation targets in favor of light sedation with more awake and alert patients will reduce the time spent on mechanical ventilation and prevent delirium (Fig. 11.1). Nursing-implemented and directed protocols/algorithms to systematically evaluate and manage both pain and agitation positively impact outcomes [4, 6].

Fig. 11.1 Rehabilitation on ECMO support. Courtesy of Jordi Riera MD PhD, Adult ECMO Program Director, Critical Care Department - Vall d'Hebron University Hospital, Barcelona, shared with patient's permission

- B: Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT). In line with institutional/national role responsibilities, combining SAT and SBT promotes communication and coordination among team members [4, 6]. Bedside patient monitoring, as a key nursing intervention, allows for the observation of a patient's effort of spontaneous/assisted breathing which is crucial in the detection and management of possible asynchronies. Adding to the ABCDEF bundle an "R" for respiratory drive control allows the operator to adapt the mechanical ventilation (MV) settings to the patient's specific circumstances and should promote spontaneous breathing as soon as possible [2].
- D: Delirium; the assessment and prevention of delirium, using validated and reliable monitoring instruments such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [7] is recommended and a cornerstone of ICU bedside nursing [4]. Delirium frequently occurs in critically ill patients and there is growing recognition about its role as a predictor of negative short- and long-term outcomes including higher mortality, increased duration of MV, longer ICU and hospital stay, and the development of PICS in survivors [5].
- E: Early mobilization and exercise to prevent or manage ICU-acquired weakness which is known to prolong mechanical ventilation/hospital stay and to increase mortality is another aspect of ICU nursing practice. Bed rest is strongly associated with neuromuscular dysfunction and physical impairment. Consequently, early rehabilitation of critically ill patients as a safe and feasible intervention: [8] with appropriate safety considerations, mobilization of adults on MV is achievable and improves cognitive/physical recovery while minimizing the risk of adverse events (Fig. 11.1) [8]. Currently, the main barriers to the implementation of rehabilitation are structural/environmental issues, and process/cultural factors rather than patient related.
- F: Family engagement and empowerment is primarily facilitated through nursing staff. Since the outbreak of the Coronavirus disease 2019 (COVID-19) pandemic in 2019, restrictive ICU visitation policies had a negative impact on both families and staff leading to increased stress levels among both groups [9]. Specifically, the lack of families at the bedside is a risk factor for developing delirium [10]. Families are an integral part of the critical care environment and essential determinants of recovery, impacting on how ICU survivors will be able to cope with PICS and with long-term or permanent functional and neurocognitive disabilities. Moreover, the family role is crucial in end-of-life decision-making and in palliative care [10].

Overarching the integration of liaison between patients, their relations, and the clinical team is the concept of family-centered care which is an interprofessional strategy (and culture). ICU nurses play an important role here as they are continuously present at the bedside, develop a privileged relationship with families, and are the key professionals to recognize and meet family needs while providing essential support and care [11].

The ABCDEF(R) is not the only bundle of care. ICU nurses have the responsibility to facilitate or implement interventions part of in evidence-based strategies, such

as care bundles aimed to reduce the incidence of preventable infections [12], particularly:

- Ventilator associated pneumonia (VAP) prevention strategies should be implemented through proper patient positioning, monitoring of endotracheal tube cuff pressure, oropharynx/endotracheal suctioning, and the management of ventilator circuits. In addition, good oral care is a basic hygiene need for the ICU patient and prevents discomfort and local or systemic complications.
- Catheter-related bloodstream infections through skin preparation before insertion, ensuring a sterile technique is implemented and providing adequate securement, wound dressing, site monitoring, and suitable management of the catheter, disposable transducers, and administration sets [13].
- Catheter-associated urinary tract infection by adopting an appropriate technique for urinary catheter placement, securement, and management, including perineal care [14].
- Nurse-driven enteral nutrition protocols optimize calories, proteins, and other nutrients intake goals in ICU patients and thereby prevent inadequate delivery [15] in this high-risk population. In parallel, glycemic monitoring and insulin administration according to nurse-managed protocols achieves safe and effective glucose control.

11.2 Prone Position

Prone position (PP) is a beneficial treatment in patients with severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (see also Chap. 29) [16]. Although PP is regarded as a non-invasive and relatively inexpensive intervention, the procedure itself is complex, associated to increased workload, requiring multidisciplinary coordination [17, 18], and full awareness of related complications and adverse events [19].

Three different categories of turning procedure have been described in the literature: manual, mechanical lift assisted, and use of specialized proning beds. Manual one is the most widely used strategy and may integrate transfer and friction-reducing devices such as slide sheets or roll-boards. It requires a skilled team of at least 4–5 members (ideally 2 caregivers per side), a team leader at the head, responsible for airway securement/management and for procedure synchronization [17, 18]. In addition, dedicated team member(s) may be required to move devices such as chest tubes [19] or extracorporeal membrane oxygenation (ECMO) tubing. Apart from these ideal configurations, if PP needs to be performed in limited human resources settings, the maneuver could be cautiously performed by as little as 3 healthcare professionals (HCP).

Developing and implementing focused institutional protocols and checklists to guide patient, team and equipment preparation, the turning procedure, and post-maneuver care are advisable to standardize the processes of PP. As such, the overall aim is to ensure consistency and improve predictability of adverse events to

maximize benefits and minimize potential harms to patients or healthcare providers [19]. Education and multidisciplinary team-training, in particular simulation, should be provided to increase staff confidence, leading to skills that are adequate to mitigate associated risks [19, 20]. During the COVID-19 pandemic, dedicated multidisciplinary and well-trained PP teams have reported a decreased strain on ICU staff and enhanced procedure safety and efficiency [21].

Adverse events and complications might be associated with bedrest or might develop during prolonged PP sessions. The implementation of protective strategies by nurses could be effective in preventing these complications or in reducing their occurrence. Facial edema, periorbital/palpebral swelling, and/or conjunctival edema/effusion are common but usually rapidly reversible once back in a supine position [17, 19, 22, 23] while other ocular complications (eventually worsened by edema) such as ocular injury/corneal abrasions may still occur.

The development of PP-related pressure sores represent the most widely cited injury [18, 22–25], being the only frequent issue with a positive association linked to the duration of PP periods [25]. ARDS patients who require PP may also have multiple risk factors which increase the likelihood of pressure injuries (PIs), such as poor peripheral perfusion due to cardiovascular instability, vasopressors/inotropes administration, acute or pre-existing organ dysfunctions, prolonged bedrest and ICU stay, suboptimal caloric intake, or comorbidities as diabetes. Although reported PIs are mostly low-grade and therefore do not require any specific interventions to gain full recovery [25, 26], healthcare providers should consider adopting a multimodal preventive strategy which includes:

- A careful continuous skin/eyes care and assessment [19, 24, 27]. Due to the high risk of injuries with multiple potential mechanisms consider the face as a key area requiring special attention in this population [24].
- The application of prophylactic dressings on at-risk areas (Table 11.1) such as bony prominences [18, 19] and on areas beneath or in contact with medical devices, in order to minimize shear stress, and redistribute pressure while also absorbing moisture [27].
- Carefully use tapes/securement devices [27].
- The use of specialized beds or mattresses and techniques/positioning devices to offload and redistribute pressure [19, 24].
- Optimizing patients nutritional status, as PIs incidence decreases in well-nourished patients [22, 27].

Implementing a long-term follow-up (see Chap. 26) might allow to spot long-term injuries which could be missed during ICU stay, increasing awareness with the aim to improve clinical practice.

Strategies to mobilize patients are commonly included in PIs prevention bundles [27] but might be limited due to the clinical need of prolonged PP and the prevention of device dislodgement [24]. Once a patient is in PP, it may be adapted, preferring reverse Trendelenburg [19, 28] and plan postural changes of head and limbs (see Table 11.1) according to institutional protocols in order to avoid brachial plexus

injury and lateral femoral cutaneous nerve compression, both of which have been described after prolonged PP.

PIs, specifically if related to the presence of medical devices, may be associated with bleeding complications if ongoing therapeutic (i.e., patients on ECLS) or high dose prophylactic anticoagulation (i.e., COVID-19 patients) is administered to patients [24].

Device displacement/withdrawal or obstruction may lead to the loss of intravascular access lines, endotracheal/tracheostomy tubes, chest drains, and other life sustaining treatments [18, 22, 23, 25] and are feared complications. In order to prevent these kind of device related complications, disconnection of not strictly essential infusions, circuits, and other monitoring devices has been suggested, during the turning procedure [19]. However, opening systems which ideally require to be kept closed to maintain their working condition and to prevent complications should be kept to a minimum balancing the following risks:

- An increased chance of developing device related infections.
- A temporary loss of vital signs monitoring; at least pulse oximetry and invasive arterial blood pressure should be preserved throughout the procedure [17, 18], and continuous ETCO2 monitoring may suggest disconnection of MV circuit or tube displacement [17, 18] so should be advisable.

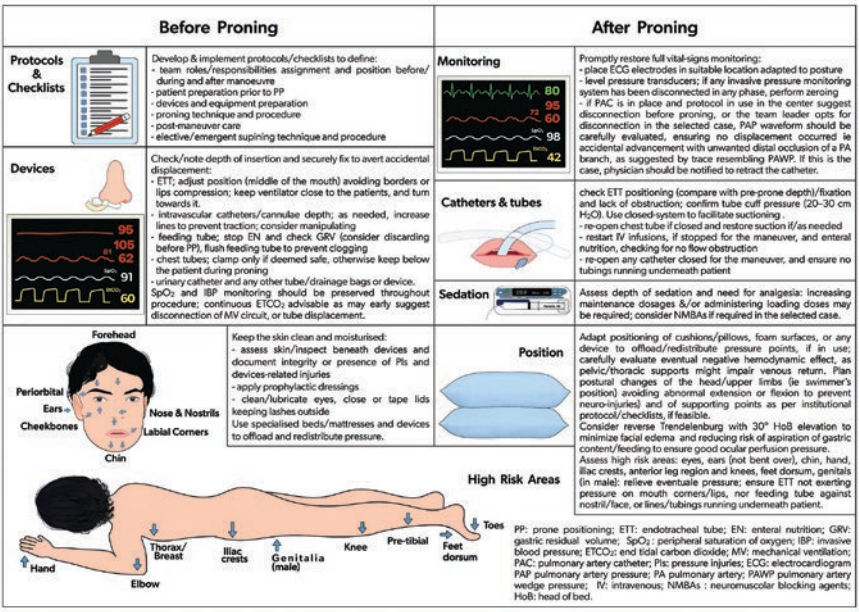
Integrity of circuits connected to devices providing life support (i.e. inotropes/vasopressors infusion pumps) needs to be preserved throughout and after the turning procedure. If necessary, intravenous lines maybe increased in length to prevent traction but careful consideration of possible consequences when manipulating the length/calibre/compliance of pressure monitoring circuits and infusion lines must be considered.

Even if rarely reported, accidental extubation is considered the most severe potential adverse event [18, 23]. Performing a meticulous assessment of the artificial airway including insertion depth should ensure its patency/function; careful securement of all devices before and after the procedure is essential to improve patients' safety (Table 11.1) [19, 25, 29]. Keeping the ventilator close to the patient and turning the patient towards it to prevent excessive tensions on the tube is a practical tip to avoid unnecessary disruption of mechanical ventilation. Overall, the whole multidisciplinary team needs to be ready for emergency repositioning of the patient back into supine position at all times and performing an eventually difficult reintubation [19, 29].

11.3 ECMO

ECMO evolved as an established support strategy improving clinical outcomes in patients with severe acute respiratory failure refractory to conventional treatments, including optimized mechanical ventilation and prone positioning [30, 31].

Table 11.1 Patient preparation and management before and after prone positioning; high-risk area for development of PP related injuries are highlighted



ECMO is considered a safe technique as long as it is performed by experienced teams in specialist centers who have the expertise of undertaking this approach [31]. Increased understanding of ECLS physiology, and advances in technologies improved circuit handling and biocompatibility, all ensure the reduction and avoidance of related complications [32]. However, ECLS remains a complex, technically challenging, high-risk, and resource-intensive treatment with significant mortality and morbidity [30, 32], and is associated with variable clinical outcomes [33].

Establishing dedicated protocols/checklists [30] that adhere to the Extracorporeal Life Support Organization (ELSO) guidelines, and formalizing a multidisciplinary team [30, 34] with clearly defined roles and responsibilities [35] is critical to limit adverse events and improve survival. To date, no international agreement exists on staffing arrangements for the bedside management of the ECMO patient nor a formal certification process for professionals. In view of this situation, the role, responsibilities, competencies, and boundaries for nurses and ECMO specialists need to consider local policies, needs, and available human resources while also respecting individual country legislation [32, 33]. The ECMO specialist is defined as the technical specialist who comes from different professional backgrounds, including perfusion, physiotherapy, and nursing, skilled in critical care, trained and experienced to manage the extracorporeal system and the clinical needs of a patient on ECLS, operating under the direction and supervision of an ECMO physician [32, 33, 36].

A recent survey [32] reported a nurse-to-patient ratio of 1:1 as the most common staffing model, with the support of a nurse acting as ECMO specialist for daily circuit management and perfusionists for technical backup [32]. This strategy appears reasonable and advisable [33] but variable nurse-to-patient ratios of 2:1 or 2:3 to 1:4 have been suggested or described [32, 35]. Cohorting ECMO patients might optimize management and resources allocation [37].

No matter what caregiver model is implemented, ECLS increases workload and extends responsibilities for nurses, being the health care professional providing 24/7 bedside care. Furthermore, closely monitoring of the ECMO patient system and their mutual interactions, while responding to conventional and specific requirements, and always being ready to deal with emergencies and complications emphasizes the complexities in looking after this patient group [32, 38].

Continuing standardized and specialized multidisciplinary education and training involving every member of the ECMO team including theoretical and practical aspects of ECMO support [35, 38, 39] are mandatory to acquire the advanced skills and knowledge required to provide both, bedside effective/safe care for an ECMO patient and monitoring/management of the ECMO circuit [32, 35–38, 40].

Providing nursing activities could be challenging in the ECMO patient, but daily care remains the key to ensure hygiene, improve comfort, and prevent or identify complications such as infections, pressure injuries, bleeding, and cannula/circuit related problems [41, 42]. Specific protocols including safety measures and a careful approach implemented by trained health care professionals may limit the occurrence of related adverse events [38].

The main medical complications include bleeding, thrombosis, and hemolysis [43]. Due to systemic anticoagulation basic interventions, such as oral care, may induce severe bleeding [42]. Consequently, nursing procedures should be undertaken with caution and those not strictly necessary interventions avoided. Continuous monitoring of coagulation status/hemolysis parameters allows for the prevention and early identification of impending complications. Usually repeated and multiple tests are performed [37, 43]. No matter the protocol for assessing the coagulation profile in use, blood sampling requires an optimal technique to avoid inaccuracy and ensure precision of results because anything else could negatively impact the anticoagulation management.

Moreover, while the ECMO machine is in operation, patients may experience specific ECLS scenarios such as drainage failure, return obstruction, and recirculation on VV configuration, and mechanical complications that any nurse caring for an ECMO patient needs to be able to recognize and troubleshoot according to the specific role(s)/boundaries in the team (*details in* Table 11.2) [38].

Complications are associated with increased morbidity and reduced survival during ECMO particularly when gas exchange and/or hemodynamic stability are impaired and may culminate in cardiac arrest in patients highly dependent on this therapy. Both a pro-active approach to promptly detect any issue through regular circuit checks [37, 38] and a re-active approach by implementing immediate and appropriate interventions/troubleshooting are required to face emergencies and major complications during this therapy [38].

Table 11.2 Basic ECMO curriculum, nomenclature[88], monitorings, and main mechanical complications potentially associated with ECMO support; some of the typical scenarios which could be associated with the physiology and pathophysiology of veno-venous extracorporeal support are also included

ECMO Curriculum, Protocols & Checklists	Develop & implement a standardized ECMO curriculum, and institutional protocols/checklists clearly defining team roles/responsibilities, focused on: - cannulation and ECMO initiation - circuit priming/assembling, alarm settings & monitoring - complications prevention, early recognition & troubleshooting - patient management, bedside care and rehabilitation - coagulation and anti-coagulation management - intra-extrahospital ECMO transportation - coming off ECMO emergently/emergent circuit replacement - ECMO weaning - clinical audit for major adverse events - ECMO program evaluation	**ECMO settings & monitorings**	RPM: pump speed, generating the EBF, depending on preload and afterload with CPs; EBF (in LPM) is read through a flowmeter. SGF or FGF: gas flow to the ML in (in LPM). FdO_2 or FsO_2: O_2 fraction of the SGF (0.21-1), controlled by an air/O2 mixer or gas blender. P_{INLET}: negative pressure at CP inlet; negative pressure also exists in drainage cannula and drainage cannula tubing. P_{PRE} (or $P_{PRE(AR)}$) positive pressure at ML inlet. P_{POST} (or $P_{POST(AR)}$) positive pressure at ML outlet; P_{POST} < vs P_{PRE}. ΔP: pressure gradient between ML inlet/outlet, calculated as ΔP = P_{PRE} - P_{POST}. ΔP/EBF ratio suggests ML resistances. $SpreO_2$: O_2 saturation at ML inlet. $SpostO_2$: O_2 saturation at ML outlet.
Drainage Insufficiency	Drainage insufficiency or drainage failure occurs when venous return to drainage cannula does not match with drainage pressure at cannula holes, due to excessively negative pressures and/or lack of return. Vena cava collapses around drainage cannula, temporarily occluding drainage baskets. P_{INLET} severely decreases and EBF becomes erratic, and ECLS inconsistent. Drainage line and cannula could vibrate or swing ("chatter"). Determinants: - absolute/relative hypovolemia - increased IAP &/or ITP (tension PTX, cardiac tamponade, IAH) - cough, asynchronies and agitation - obstruction of drainage line and/or drainage cannula, and obstruction involving cannulated vessel.	**Air entrance**	Air could enter within ECMO circuit, from microbubbles to massive embolism depriming CP, leading to an "air-lock". Atmospheric air could be mainly aspirated if any break/disconnection occurs in the negative pressure side of circuit, or through an open port of a CVL. Moreover, air bubbles could develop if blood is exposed to excessively negative pressures, due to cavitation.
		Pump Failure	Pump failure occurs when CP is not able to provide the EBF: lack of EBF results in loss of support. CP may fail due any complication involving pumphead (disengagement, thrombosis or massive air embolism), or involving console or drive unit (lack of power & exhausted battery; electronic/mechanical dysfunction).
Recirculation	Suction of highly oxygenated/decarboxylated blood from return to drainage cannula on VV-ECMO. RF, calculated as RF = RBF/EBF, does not contribute to support to gas exchange, decreasing effectiveness of ECLS. RF rises increasing pump speed and reducing distance between cannulae. The higher the RF, the higher the $SpreO_2$; colour of blood within drainage line will appear similar to blood within return line (brighter red).	**Membrane Lung & Gas Line Failure**	Progressive or acute formation of clots/thrombi and fibrin deposition within ML reduces available area for extracorporeal gas exchange, impairing blood oxygenation/decarboxylation effectiveness; $P_{POST}O_2$ & $S_{POST}O_2$ decrease. Clots, thrombi and fibrin could be noticed transilluminating explorable portions of ML ("flashlight test"). As higher resistances impair EBF, P_{PRE} increases while P_{POST} decreases, augmenting ΔP. Moreover, systemic coagulopathy or hemolysis, otherwise unexplained or not fully explained, may arise if extensive ML thrombosis. Any issue within the gas line providing FGF to ML (improper FGF/FdO_2 setting, accidental disconnection, source exhaustion) will impair gas transfer, independently from ML function. Moisture may collect inside gas fibers, reducing extracorporeal CO_2 removal, requiring regular clearance (ML "sighing").
Return Obstruction	Increased resistance to blood return due to obstruction to the outflow distal to CP. Obstruction could be intraluminal (i.e. clot/thrombus) or extraluminal (i.e. kinking, compression, tension PTX or tamponade) and may occur in the return line, cannula, or vessel, increasing P_{PRE}/P_{POST} and reducing ΔP; obstruction in the ML increases P_{PRE} and decreases P_{POST}, increasing ΔP (see ML failure). Return obstruction impairs EBF so ECLS effectiveness.		
Circuit disruption	Breakage of the circuit: if occurring on the pre-pump side causes air entry; if occurring post-pump induces blood loss. Disruption of any main component of the extracorporeal circuit requires coming off ECMO emergently to prevent additional air entry/blood loss and manage rupture/replace the component or the circuit: ECLS will be suddenly interrupted.		
Accidental decannulation	Unintended removal or significant displacement (exposing baskets) of the ECMO cannula/ae: if involving drainage cannula air enters into the circuit; if involving return cannula leads to exsanguination. Blood loss from the insertion site occurs in both situations. Accidental decannulation requires coming off ECMO emergently: ECLS will be suddenly interrupted.		

Table 2: Basic ECMO curriculum, nomenclature, monitorings, and main mechanical complications potentially associated with ECMO support; some of the typical scenarios which could be associated with the physiology and pathophysiology of veno-venous extracorporeal support are also included. ECMO: extracorporeal Membrane Oxygenation; RPM: revolutions per minute; CP(s): centrifugal pump(s); EBF: extracorporeal blood flow; LPM: liters per minute; SGF: sweep gas flow; FGF: fresh gas flow; ML: membrane lung (artificial lung); FdO_2: device oxygen fraction; FsO_2: oxygen fraction in the sweep gas; ECLS: extracorporeal life support; IAP: intra-abdominal pressure; ITP: intra-thoracic pressure; PTX: pneumothorax; IAH: intra-abdominal hypertension; VV: veno-venous; RF: recirculation fraction; RBF: recirculating blood flow; CVL: central venous line.

Note: providing a detailed discussion on how to prevent, early detect and manage mechanical complications and pathophysiology of ECLS is out of the scope of this chapter.

ECMO extracorporeal membrane oxygenation, *RPM* revolutions per minute, *CP(s)* centrifugal pump(s), *EBF* extracorporeal blood flow, *LPM* liters per minute, *SGF* sweep gas flow, *FGF* fresh gas flow, *ML* membrane lung (artificial lung), FdO_2 device oxygen fraction, FsO_2 oxygen fraction in the sweep gas, *ECLS* extracorporeal life support, *IAP* intra-abdominal pressure, *ITP* intra-thoracic pressure, *PTX* pneumothorax, *IAH* intra-abdominal hypertension, *VV* veno-venous, *RF* recirculation fraction, *RBF* recirculating blood flow, *CVL* central venous line

Note: Providing a detailed discussion on how to prevent, early detect and manage mechanical complications and pathophysiology of ECLS is out of the scope of this chapter

Before moving patients on ECMO for nursing or rehabilitation purposes, medical procedures, or transports, carefully proceed by securing the cannula and the tubing [31, 37]. Accurate dressings of cannula insertion sites may prevent infections, reduce topical bleeding, and help secure catheters [35, 38].

Whenever feasible during mobilization, 1-2 (perfusionist and/or ECMO specialists) should take care of the circuit to prevent complications including circuit disruption or accidental decannulation and to ensure periprocedural drainage effectiveness and continuous stability of extracorporeal blood flow (EBF). At times, small adaptations of a patient's position in bed can prevent persistent impairment of ECLS [41]. Implementing physical rehabilitation and early mobilization is

considered feasible and safe in this patient population, as long as performed by multidisciplinary teams, trained and skilled. These interventions might be associated with improved outcomes [43].

If refractory hypoxemia persists despite optimal ECMO support, PP might be a reasonable and effective option [44, 45]. Cannula displacement is the most feared complication during simultaneous PP and ECMO but, to the best of our knowledge, so far no occurrence of this complications has been reported [45]. Even if bleeding at cannulation site is a common phenomena [44–46] it is possibly unrelated to PP. However, a drop in EBF could be observed during this procedure [44, 45] requiring the operator to preserve cannula tubing patency by using devices that avoid compression. Furthermore, prompt PP reversal to the supine position may be required if EBF is severely impaired after the maneuver.

It is advisable to mobilize the patient and perform nursing interventions when physicians and perfusionist are readily available to provide support. Titrating mechanical ventilation and EBF settings may be required to cover for increased oxygen demands. Similarly, with the same rationale patient sedation requirements may need to be adjusted [41].

11.4 Conclusions

ICU nurses caring for critically ill patients with ARF or ARDS undergoing mechanical ventilation, and eventually PP and ECLS, need to be aware of the unique their complex needs, requiring extensive knowledge of both pathophysiology and therapies/support strategies, advanced technical skills, but also soft caring skills, to provide optimal care to this population, and to the families, in order to contribute to short- and long-term functional outcome improvement.

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Closed-Loop Ventilation Modes

12

Jean-Michel Arnal, Dirk Schaedler, and Cenk Kirakli

12.1 Introduction

The term "closed-loop ventilation modes" refers to modes that automatically adjust certain ventilator settings, based on one or more feedback signals. The general principle of operation is as follows: The ventilator measures some of the patient's physiological variables, compares them to the corresponding targets set by the user, then automatically adjusts certain ventilator settings to reduce the difference between the actual and target values (negative feedback). The controller input must be a physiological variable that is reliable in all types of patients, easy to measure, cheap, and—if possible—noninvasive. Measurements are usually made over several breaths and averaged, to avoid the effect of outlier values. The targets can be set by the user or determined by an algorithm, either fixed or variable according to some other condition. The automatic adjustment of ventilator settings takes place slowly, breath-by-breath or over several breaths. When using a closed-loop ventilation mode, clinicians need to set the targets, rather than the actual ventilator settings; this requires a different knowledge and mindset. Monitoring in closed-loop ventilation modes is similar to in conventional modes, but provides additional information

J.-M. Arnal (✉)
Service de Réanimation, Hôpital Sainte Musse, Toulon, France

Medical Research and New Technologies, Hamilton Medical AG, Bonaduz, Switzerland
e-mail: jean-michel@arnal.org

D. Schaedler
Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Kiel, Germany

C. Kirakli
Intensive Care Unit, Dr. Suat Seren Chest Diseases and Surgery Training and Research Center, University of Health Sciences, Izmir, Turkey

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about the dynamic changes in the patient's condition. Continuous adaptation of the ventilatory support to the changes in the patient's respiratory mechanics, spontaneous activity, and effort has several potential benefits. It may result in more time spent in optimal ventilation and oxygenation ranges, and adequate ventilation support that can reduce the risk of ventilator-induced lung injuries, patient-ventilator asynchrony, and over- or under-assistance. Ultimately, clinical outcomes—such as duration of mechanical ventilation and mortality—may be improved. The potential risks lie in a lack of training and experience, leading to inappropriate targets being set and inadequate monitoring.

Mandatory Minute Ventilation (MMV), Adaptive Support Ventilation (ASV), INTELLiVENT-ASV, and Smartcare/PS are all closed-loop ventilation modes that are commercially available today and will be explained in detail in this chapter.

12.2 Mandatory Minute Ventilation

Mandatory Minute Ventilation (MMV) is the first closed-loop mode that was described in 1977 to overcome certain ineffective features of intermittent mandatory ventilation [1]. MMV is a pressure-support mode that guarantees a target minute ventilation set by the user. If the patient's spontaneous ventilation does not reach the target minute ventilation, the ventilator either increases the level of pressure-support (PS) or adds a mandatory breath, depending on the manufacturer. Conversely, when the patient's spontaneous ventilation exceeds the target minute ventilation, the ventilator decreases PS. MMV is only available on a few ventilators today and is seldom used. The main risk is that target minute ventilation can be achieved with very large tidal volumes (VT) that carry a risk of lung injury or with a combination of very low VT and a high respiratory rate (RR) that carries a risk of dead-space ventilation and under-assistance. At the current time, the value of MMV for facilitating weaning is unclear [2].

12.3 Smartcare/PS

12.3.1 Principle of Operation

SmartCare/PS controls the level of PS applied in pressure-support ventilation mode. None of the other ventilator settings are changed by the system. Activation of SmartCare/PS requires a set of conditions (e.g. $EtCO_2$ monitoring is active, PEEP between 5 and 20 cm H_2O, apnea ventilation active) If started, SmartCare/PS attempts to bring the patient into a so-called respiratory comfort zone and keep her/him there. This means that PS maintains a minimum VT of greater than 300 ml with an end-tidal partial pressure of CO_2 ($PetCO_2$) below 55 mm Hg, and a spontaneous RR of between 15 and 30 breaths per minute. Once a patient stabilizes in the

comfort zone, PS is decreased stepwise to a target PS. The target PS depends on the artificial airway, the humidification system used, and whether automatic tube compensation is activated or not. The pace at which SmartCare/PS decreases PS depends on the actual PS. The higher the PS value, the slower the decrease, and vice versa. If the patient is still stable on the target PS and the user-defined limits for the fraction of inspired oxygen (FiO_2) and the positive end-expiratory pressure (PEEP) are not exceeded, SmartCare/PS performs an automated spontaneous breathing trial (SBT). If the SBT is completed successfully, SmartCare/PS displays a message on the ventilator screen recommending the separation of the patient from the ventilator [3].

12.3.2 Monitoring

It is essential to monitor the weaning progress in SmartCare/PS. Based on our experience, we recommend setting up a special SmartCare page on the ventilator showing graphs for the weaning diagnosis and the applied PS. This page can be used during the clinician's rounds to get an overview of the weaning performance during the last few hours or days (Fig. 12.1). Furthermore, many SmartCare/PS details can be transferred to a patient data management system (PDMS). On a special weaning page in the PDMS, the whole weaning approach can be assessed more easily by integrating more weaning variables (e. g., sedation scores, nutrition, mobilization status, etc.).

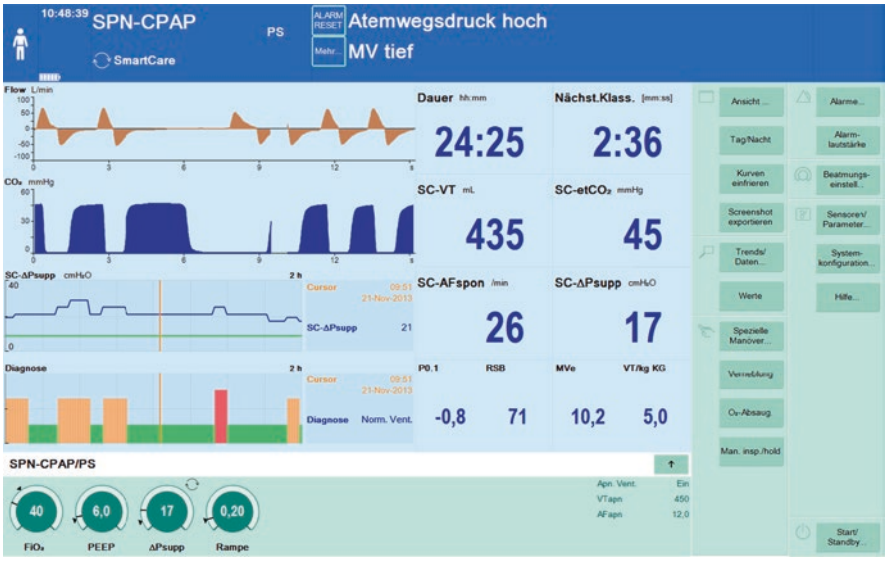

Fig. 12.1 An example of a special weaning page on the V500 ventilator (Dräger)

12.3.3 Evidence

In a multicenter randomized controlled trial in five European university hospitals, Lellouche et al. compared SmartCare/PS to the usual care, whereby the usual care differed among the five study sites. The ventilation time was significantly lower in the SmartCare/PS group compared to the control group (7.5 vs. 12 days, $p = 0.003$) [4]. Motivated by this impressive result, Schädler et al. performed a single-center randomized controlled study involving 300 patients. In contrast to the study by Lellouche et al., a standardized weaning protocol was used in the control group. No significant differences were found between the groups in terms of total ventilation time ($p = 0.178$) [5]. Similarly, neither two smaller single-center studies [6, 7] nor one pilot multicenter randomized controlled trial [8] detected a significant difference in ventilation time. However, several meta-analyses have shown a beneficial effect of automated weaning on ventilation time (especially for SmartCare/PS) [9, 10]. A recent Bayesian network meta-analysis showed clearly that automated weaning modes (regardless of the technology used) decrease ventilation time [11].

In conclusion, weaning with SmartCare/PS is at least as efficient as the gold-standard weaning protocol. Further developments should improve the practical use of the system (complicated setup, automated restart of SmartCare/PS after it has been stopped) and the technology (integration of physiological lung models, automated control of additional ventilator settings). Furthermore, the automated weaning system should interact with the PDMS with the aim of gaining more insights into the patients' medical information (e. g., blood gas analyses, radiological findings, medical diagnoses) and achieving better support throughout the whole weaning process.

12.4 Adaptive Support Ventilation

ASV is a closed-loop ventilation that combines an adaptive pressure-controlled ventilation in passive patients and an adaptive pressure-support ventilation in spontaneously breathing patients. The advantages of this mode are that it optimizes the patient's work and force of breathing, decreases the workload of ICU staff, and improves patient safety and comfort.

12.4.1 Principle of Operation

The ASV algorithm was initially based on the minimal work of breathing according to Otis' equation [12] and later modified to introduce the minimal force of breathing according to Mead's equation [13, 14]. ASV assesses the patient's respiratory mechanics by measuring the expiratory time constant (RCexp) breath-by-breath and then determines a VT-RR combination for any given minute ventilation set by the clinician with the aim of minimizing the work and force of breathing (Fig. 12.2). As a consequence ASV automatically selects a low VT and high RR in restrictive

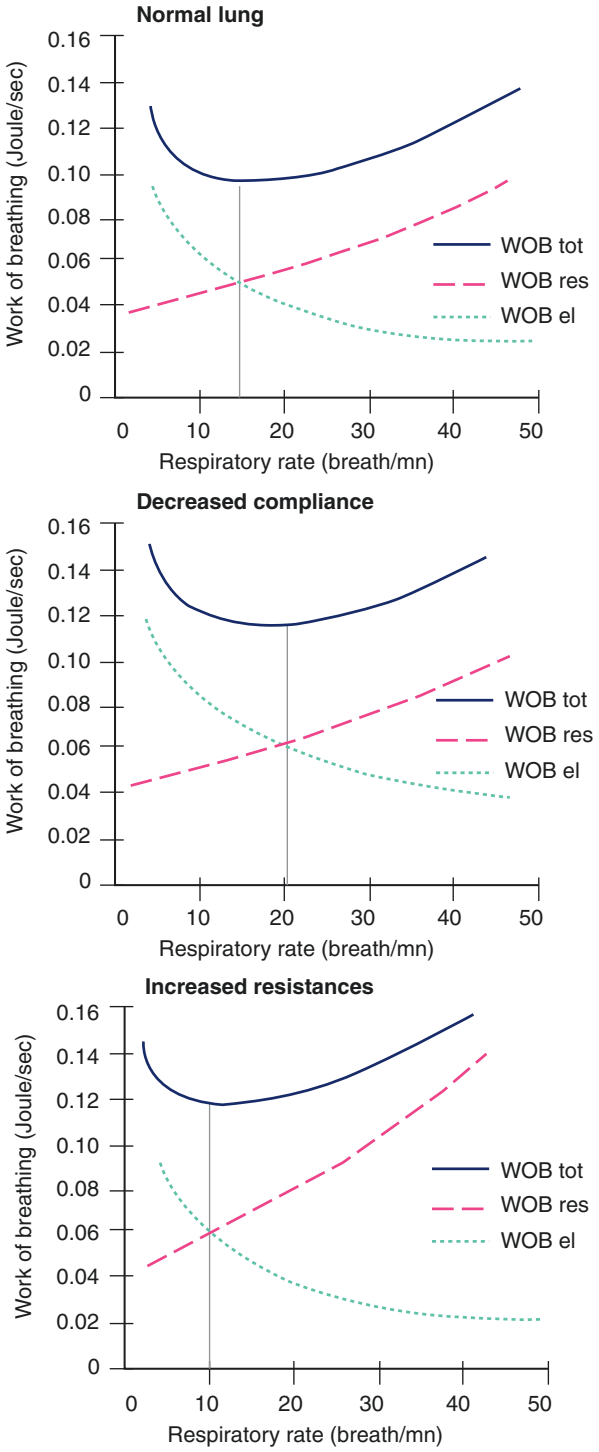

Fig. 12.2 According to Otis equation, for a given minute ventilation, the total work of breathing (WOB tot) is the sum of resistive WOB (WOB res) and elastic WOB (WOB el) and depends on the respiratory rate with a U-shape. ASV select the respiratory rate associated with the least WOB tot. This optimal respiratory rate is higher in case of decreased compliance and lower in case of increased resistance as compared to a normal lung condition

pathologies and the opposite in obstructive pathologies. In actively breathing patients, it delivers pressure-supported breaths and adjusts PS to reach the optimal VT. Therefore, PS decreases automatically in preparation for weaning as the patient's effort increases.

12.4.2 Settings and Monitoring

Initial settings and adjustments (passive patients)

- Target minute ventilation expressed in % of ideal body weight (IBW) (MinVol%): Set at 100%, which equates to 100 ml/kg IBW/min.
- Pressure limit: Set at 30 cm H_2O (may be increased in severe obstructive diseases).
- PEEP and FiO_2: Require manual setting according to transcutaneous oxygen saturation (SpO_2) or arterial partial pressure in oxygen (PaO_2).
- Adjustments must be made to MinVol% in steps of 10% according to $PaCO_2$.

Initial settings and adjustments (spontaneously breathing patients)

- MinVol%: Set at 100%.
- Pressure limit: Set at 30 cm H_2O (may be increased in severe obstructive diseases).
- PEEP and FiO_2: Require manual setting according to SpO_2 or PaO_2.
- Adjustments must be made to MinVol% in steps of 20% according to patient effort and RR.

Respiratory mechanics such as RCexp, compliance, and resistance must be monitored to understand the underlying pathology and adjust the ventilation strategy accordingly. In addition to VT/IBW, peak and plateau pressure, driving pressure, and PS-levels must also be monitored closely to avoid ventilator-induced lung injury.

12.4.3 Weaning

If the patient has acceptable PEEP and FiO_2 levels and is ready for weaning, MinVol% is set to 25% for a spontaneous breathing trial. If the PS-level is acceptable (below 10–12 cm H_2O) at the end of the trial (30 min to 2 h) and there are no other contraindications, the physician should consider extubation.

12.4.4 Evidence

Several studies have investigated the advantages of ASV over conventional modes in both passive and actively breathing patients in medical, surgical, and neurological ICU. They reported a decreased duration of weaning or the entire ventilation period

[15–19]. There is also some evidence that ASV can select individualized VT-RR combination, and decrease the metabolic load and mechanical power delivered to the patient when compared to conventional ventilation modes [20–22]. There are ongoing studies to investigate the effect of ASV in ARDS patients and the pediatric population (NCT03715751, NCT03930147).

12.5 INTELLiVENT-ASV

INTELLiVENT-ASV is an evolution of the ASV mode, which provides fully automatic control of ventilation and oxygenation settings for both passive and spontaneously breathing patients, adjusting to changes in the patient's respiratory mechanics, spontaneous activity, and effort, as well as oxygenation requirements. INTELLiVENT-ASV also incorporates an automated weaning protocol.

12.5.1 Principle of Operation

In terms of ventilation support for passive patients, INTELLiVENT-ASV automatically sets the target minute volume based on the difference between the measured $PetCO_2$ and the target $PetCO_2$ set by the user. In spontaneously breathing patients, INTELLiVENT-ASV automatically sets target minute volume according to the difference between the patient's actual RR and an optimal RR target range determined by the ASV algorithm. Once the target minute volume has been established, the ASV controller selects an optimal combination of VT and RR, then delivers either an adaptive pressure-control breath in passive patients or an adaptive pressure-support breath in spontaneously breathing patients (Fig. 12.3).

In terms of oxygenation support, INTELLiVENT-ASV automatically adjusts PEEP and FiO_2 based on the difference between the measured SpO_2 and the target SpO_2 set by the user. The oxygenation controller uses the same rules for passive and spontaneously breathing patients. Changes to PEEP and FiO_2 are made according to PEEP-FiO_2 tables; the NIH low and high PEEP-FiO_2 tables are used for increasing and decreasing the treatment, respectively [23, 24].

12.5.2 Settings and Monitoring

Initial settings involve activating the controller, selecting the patient's condition, and adjusting the $PetCO_2$ and SpO_2 targets. Based on the patient condition selected (normal, ARDS, chronic hypercapnia, or brain injury), the ventilator suggests default target ranges appropriate for that condition. However, the user has the option of changing these targets. The user also needs to set the maximum peak pressure, the minimum FiO_2, and the range of PEEP. Finally, as in any closed-loop mode it is crucial to set the alarms correctly to ensure that the user is alerted if a sudden event occurs.

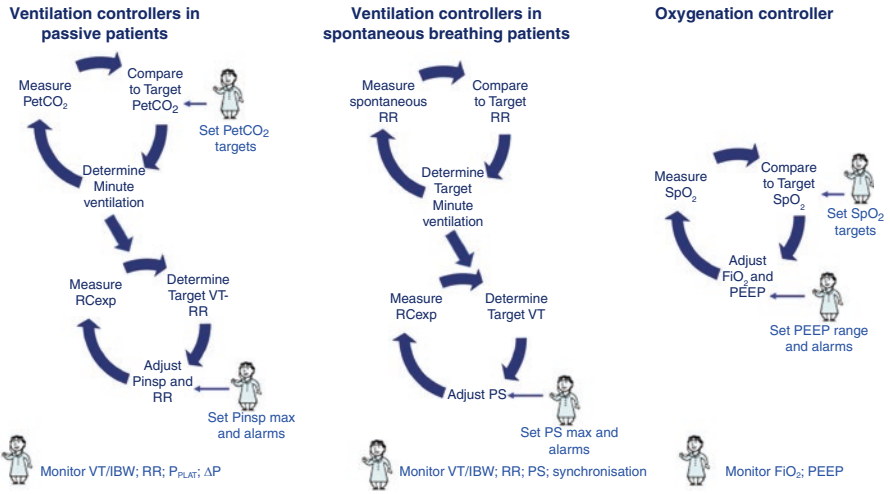

Fig. 12.3 Principle of operation of INTELLiVENT-ASV. A first controller determines the target minute ventilation and the ASV controller then selects the inspiratory pressure and respiratory rate. *PetCO*$_2$ end-tidal CO_2 measured by a mainstream sensor, *RCexp* expiratory time constant, *VT* tidal volume, *RR* respiratory rate, *Pinsp* inspiratory pressure, *IBW* ideal body weight, *PPLAT* plateau pressure, ΔP driving pressure, *PS* pressure support

In passive patients, monitoring of the respiratory mechanics (compliance, resistance, and RCexp) facilitates an understanding of the patient's lung condition, while monitoring of VT/IBW, plateau pressure, total PEEP, and driving pressure ensures that the ventilation delivered aligns with a protective ventilation strategy. In terms of oxygenation, SpO_2 provides no added value as it is a target and mostly within the target range, whereas FiO_2 and PEEP are dependent variables to monitor.

12.5.3 Weaning

INTELLiVENT-ASV has an automated weaning protocol called Quick Wean, which must be activated by the user when the patient is spontaneously breathing and stabilized. Once activated, the ventilator gradually reduces PS and screens the readiness-to-wean criteria. When the readiness-to-wean criteria are met for a certain duration, the ventilator switches to an automatic weaning trial by reducing PEEP and PS. The weaning trial is closely monitored and can abort at any time if some of the variables are outside target ranges. Conversely, if the weaning trial is successful after a given duration, it will stop automatically and a message will be displayed. The clinician should then screen the extubation criteria. Settings, duration, and all the criteria to start and abort the weaning trial are configurable by the user.

12.5.4 Evidence

INTELLiVENT-ASV has been available on certain Hamilton Medical ventilators since 2010. Several studies have tested its efficacy and safety in comparison to conventional modes in passive and spontaneously breathing patients, both in the medical ICU and after cardiac surgery [25–29]. Based on a breath-by-breath analysis over a variable duration of ventilation, the time spent in desirable ranges in INTELLiVENT-ASV was shown to be the same as or higher than in conventional modes, suggesting both reliable efficacy and safety. Feasibility studies in the ICU and in post-cardiac surgery patients demonstrate that it can be used in most patients with very few failures, including severe COVID-19 ARDS patients [29, 30]. Preliminary data show good outcomes in terms of ventilation duration [28, 30, 31] but there has been no large randomized controlled trial focusing on outcomes to date. One large multicenter randomized controlled trial is currently ongoing (NCT04593810). Several studies have demonstrated a decrease in the number of manual ventilator settings when using INTELLiVENT-ASV as compared to conventional ventilation modes, which may represent a reduction in the caregivers' workload [26, 27, 30–32].

12.6 Conclusion

Several closed-loop ventilation modes are available for mechanically ventilated ICU patients. All of them are based on a physiological algorithm or knowledge-based. It is important that clinicians fully understand the way it "reasons," in order to set the targets correctly, monitor the patients adequately, and use the tool efficiently to take timely medical decisions. Preliminary studies show these modes' potential to provide continuous lung-protective ventilation and also decrease ventilation duration, all with what appears to be minimal risk. However, further evidence is needed to fully assess their value. Future evolution of these modes will probably integrate machine learning and artificial intelligence tools, in order to further enhance the safety and individualization of mechanical ventilation.

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Airway Pressure Release Ventilation

13

Niklas Larsson

13.1 Introduction

Airway pressure release ventilation (APRV) is a time-cycled, pressure-limited mode of mechanical ventilation. Unrestricted spontaneous ventilation is possible, independent of machine-controlled breaths [1]. The APRV mode utilizes continuous positive airway pressure (CPAP) on two different pressure levels. As the name of the mode suggests, long intervals with the higher pressure level are interspaced by short releases to the lower pressure level. Because the machine-delivered airway pressures are continuous, the patient can breathe spontaneously and freely during any part of the breathing cycle. In practice, spontaneous breathing is limited to the phase spent on the higher pressure, since the patient will exhale by an airway pressure gradient during the short phase with low pressure.

Ventilator controls in APRV differ from other modes of ventilation. The two different pressure levels, PHigh and PLow, are set independently. The time spent on each pressure during every breathing cycle is set by THigh and TLow. Together, these four parameters determine driving pressure, breathing frequency, and I:E ratio. Correctly set, TLow is sufficiently short to avoid complete exhalation. An appropriate auto-PEEP is thus retained, and the actual PEEP, as well as the machine-controlled tidal volume, are both derived primarily from time TLow, rather than the set pressures. If incorrectly set up, APRV can deliver conventional pressure control ventilation, though with settings more difficult to manage (Fig. 13.1).

N. Larsson (✉)
Council of Västerbotten, Anaesthesia and Intensive Care, Umeå, Sweden
e-mail: niklas.larsson@regionvasterbotten.se

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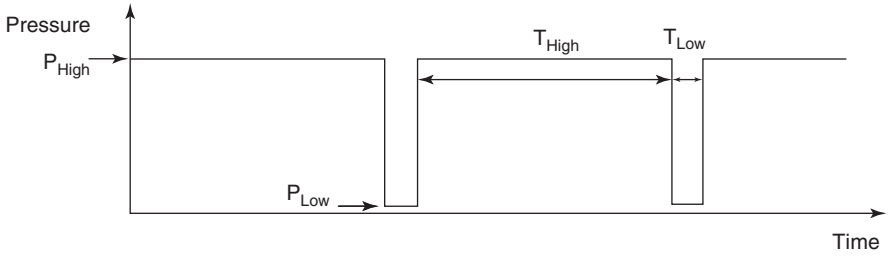

Fig. 13.1 Schematic pressure curve in APRV. A relatively long time spent on a high continuous pressure is interspaced by short releases of pressure to facilitate the mechanical breaths. The patient can freely breathe continuously during the mechanical breathing cycle

13.2 Physiology

APRV is fundamentally different from other types of mechanical ventilation from a physiological point of view. Instead of delivering a relatively short inhalation by an increase in pressure, the lungs in APRV are kept expanded for long periods of time. The periods with high pressure are interspaced by short exhalations, followed by immediate inhalations as the higher pressure level is restored [2]. The long time spent with expanded lungs can recruit atelectatic lung tissue and allows for diffusion of gas between dead space and the alveolar space [3–5]. As diffusional gas exchange occurs, patients with optimized settings in APRV can increase their CO_2 elimination in relation to alveolar ventilation [6]. This might confer lung protection as less alveolar ventilation decreases the potential for induction of ventilator induced lung injury, VILI [7]. Animal experiments suggest that APRV may be lung protective by minimizing tidal derecruitment and by optimizing tidal alveolar deformation to preserve homogeneity in lung architecture [8, 9].

13.3 Indications

APRV can significantly improve oxygenation in patients with severe hypoxemia [6, 10, 11]. Regarding patient outcomes, the role for APRV remains largely unproven [10, 12]. APRV compared to low tidal volume ventilation has been shown to improve oxygenation and reduce ICU length of stay [13]. APRV has also been showed to improve hemodynamics, as well as lung function [11]. A publication of single center data compared to a systematic review suggested that systematic application of APRV in a center with well-trained staff may offer protection from lung injury [14]. However, there are no large multicenter studies comparing APRV to conventional ventilation, and a clear definition for how APRV should be optimally delivered is not yet established. Interpretation of published reports is hampered by variations in practice and ventilation protocols [5].

There are no absolute indications for APRV. APRV may be considered in cases of refractory hypoxemia or in patients deemed in need of recruitment. As APRV allows for spontaneous breathing efforts independent of machine-triggered breaths, the mode may be used for patients with earlier mechanical dyssynchrony with ventilatory support, or for patients on the verge of conversion from controlled to assisted spontaneous ventilation. Furthermore, APRV can be used to reduce demand for sedation and for muscle relaxants [11]. To guarantee availability of APRV expertise in very complicated patients, APRV may be used liberally in other patients to gain experience. Generally, ventilation with APRV is easier to set up in patients with restrictive lung disease or healthy lungs, compared to those with obstructive lung diseases.

13.4 Settings

THigh, PHigh, TLow, and PLow must be set in relation to each other in order to achieve the desired physiological effect. As the individual settings are adjusted, the result of any change will always be based on the interaction between time and pressure.

13.4.1 PHigh

PHigh is generally set to achieve recruitment and inhalation to a point where comfortable spontaneous breathing is still possible. Usually this pressure is close to (or somewhat lower than) the plateau pressure (PPlat) in conventional ventilation. For most patients, both children and adults, a PHigh between 20 and 25 cm H_20 is appropriate. Some patients, for example, the morbidly obese or those with reduced chest wall or abdominal compliance, may need higher pressure. The initial setting of PHigh may be approximated from PPlat. Titration of PHigh may then be facilitated by close observation of the patients spontaneous breathing efforts. A correctly set PHigh will yield an optimal compliance. Patients may be allowed to quietly use abdominal muscles to facilitate exhalation. Activation of abdominal muscles during inspiration can signify that the patient is trying to defend herself/himself against an excessive PHigh. If the patient needs to activate auxiliary breathing muscles, a change in PHigh should be considered. A too low PHigh will lead to derecruitment and loss of compliance. However, a PHigh set too high will lead to reduced compliance due to overdistension. Therefore, labored breathing may be a sign of either too high or too low PHigh, and sometimes a trial of either an increase or a decrease of pressure is the only way to identify the likely problem.

Optimal setting of PHigh should result in maximal recruitment without overdistension. This will also optimize gas exchange and ventilation/perfusion matching. Conversely, both hypoxia and hypercapnia may be caused by either derecruitment due to a too low PHigh or overdistension with increased alveolar dead space due to a too high PHigh. Evaluation of PHigh should be done with close attention to the

effect on gas exchange, and problems with hypoxia or hypercapnia should always prompt an evaluation of PHigh.

13.4.2 THigh

The duration of time spent at PHigh is set by THigh. In APRV, the THigh phase should be as long as possible, since recruitment takes place over time, and a too short PHigh will have less effect for optimal lung recruitment. Conversely, THigh is the principal determinant of the frequency of releases. A THigh set too long will lead to insufficient ventilatory support. For most adult patients, THigh is initially set between 4 and 6 s.

With the exception of patients with obstructive lung diseases, THigh lower than 4 s in adults is almost never consistent with APRV physiology, as time on PHigh will be insufficient to achieve stabilization of the recruited lung of significant diffusion of gases between alveoli and the dead space. As a consequence of the long inspiratory time, set respiratory rate is very limited in APRV. Patients with severe airway obstruction may occasionally need shorter THigh because their prolonged expiratory phase includes a slow decrease of pressure and necessitates more frequent releases due to the long time spent on PLow.

In general, THigh should be set as long as possible (usually >90% of the time in the breathing cycle) while still avoiding hypercapnia or exhaustion of breathing muscles. Prolonging THigh will help stabilize lung recruitment and facilitate gas exchange by diffusion. However, as prolongation of THigh will reduce the frequency of releases, close attention must be paid to arterial CO_2 levels and sign of muscle fatigue as THigh is extended. A rise in arterial CO_2 should prompt a trial of shorter THigh unless THigh is near 4 s. In that case, one should consider if THigh is too short to achieve recruitment with gas exchange through diffusion.

13.4.3 PLow

PLow is often not used as a target pressure since actual PEEP will be determined by intrinsic PEEP. Thereby, intrinsic PEEP is a function of TLow, rather than the set pressure. Accordingly, PLow may routinely be set to 0 cm H_2O to minimize resistance to expiratory air flow and maximize peak expiratory flow rate, PEFR. The intrinsic PEEP from a short TLow will be significant. Routine measurement of the magnitude of intrinsic PEEP may not be relevant as the magnitude of intrinsic PEEP will be individualized from effects of compliance and airway resistance.

Flow is possible during the PLow phase as it is essentially a low level of CPAP. Spontaneous breathing is thus possible. Due to the short duration of the release to PLow, there is generally insufficient time on PLow to allow for any coordinated breathing efforts during this phase.

13.4.4 TLow

TLow is the time allowed for the release phase to the lower pressure level. As the name of the mode implies, ventilation in APRV is created by releases during TLow. TLow is limited to a very short period to avoid derecruitment and to limit the exhaled tidal volume. A significant auto-PEEP is thus generated since a significant volume above functional residual capacity is retained in the lungs at the end of expiration. The exact titration of TLow differs between published protocols, but generally a target is set for a desired fall in expiratory flow rate. TLow is thus set to allow the expiratory flow rate to fall to a preset percentage of PEFR, usually between 50 and 75%. This practice automatically individualizes ventilation as the tidal volume exhaled will be determined by lung volume, airflow resistance, and compliance (Fig. 13.2).

The desired reduction in expiratory fall rate can consistently be used in different clinical scenarios to adapt the resulting tidal volume to patient characteristics. A fall to 75% of PEFR can be the target for ventilation in pediatrics as well as in adults with obstructive or restrictive lung diseases. Patients with obstructive lung diseases may need a greatly prolonged TLow to accomplish a targeted fall in expiratory flow rate.

13.5 Spontaneous Breathing

In APRV, spontaneous breathing is usually encouraged. A target of 50% of minute ventilation due to spontaneous breathing within the first 24 h of ventilation may be employed, as spontaneous breathing in APRV will help to preserve diaphragm function, allow for reduced sedation, and improve hemodynamics [13, 15, 16]. If there

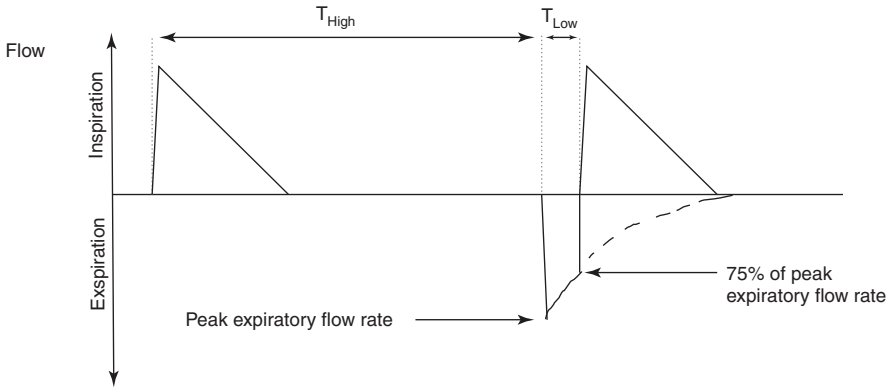

Fig. 13.2 Flow during THigh and TLow in the absence of spontaneous breathing. TLow is set to terminate exactly when expiratory flow rate falls to 75% of its peak value. The dashed line shows the theoretical continued exhalation that would occur if exhalation was allowed to continue unopposed

are no spontaneous breathing efforts, a reasonably stable patient may be briefly challenged by doubling THigh during a few minutes. This should prompt an immediate rise in arterial carbon dioxide due to low minute ventilation and thus stimulate breathing. Should this procedure fail to generate breathing efforts, a decrease in sedation is recommended. In cases with low arterial CO_2, the decrease in sedation can be combined with an increase in THigh to retain more CO_2. Once spontaneous breathing is established, it will help facilitate the setting of PHigh.

In the author's experience, APRV will almost invariably facilitate a normal gas exchange immediately after start of ventilation, even without spontaneous breaths, in patients with healthy lungs. Spontaneous breathing is almost always encouraged but when APRV is applied to severely diseased lungs, it usually takes up to 24 h to achieve adequate carbon dioxide elimination (with spontaneous breathing allowed). The initial hypercapnia may be very troublesome, even when the patient is allowed to breathe.

In the author's institution, APRV patients are virtually always allowed to breathe and the goal is usually to have 50% spontaneous minute ventilation as soon as possible. Even patients who previously have received muscle relaxants for lung protection are allowed to breathe if they are switched to APRV, though the transition in such patients may be challenging.

13.6 Weaning

When patients are stabilized and their respiratory status is improved, weaning from mechanical ventilation is possible in APRV. The initial decrease in ventilatory support is accomplished by increasing THigh, which reduces the frequency of releases and thereby diminishes the level of respiratory support. During this phase, PHigh, TLow, and PLow are monitored and titrated according to the principles above. When a maximal THigh is reached (which for many ventilators may be 30 s), the ventilator mode can be switched to CPAP set with the same PEEP as PHigh and 0 pressure support. If this is tolerated by the patient, further weaning is accomplished by fractional decreases of CPAP until the patient is deemed ready for extubation.

13.7 Conclusion

APRV utilizes settings that are conceptually very different from conventional mechanical ventilation. To benefit from the theoretical advantages of APRV, settings must be managed with a specific aim to bring about the special physiological effects APRV may achieve. In fact, even though all aspects of conventional ventilation such as tidal volume and frequency, auto-PEEP, I:E and driving pressure are derived from the APRV settings, operators are strongly encouraged to set aside the conventional parameters. Instead, focus on the specific APRV settings (P and T High and Low, respectively) should be maintained to maximize the physiological gain from using the mode. However, to date there is no unequivocal evidence of outcome benefit for APRV. Neither is there a consensus on optimal settings.

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Part II

Clinical Scenarios

Acute Hypoxaemic Respiratory Failure and Acute Respiratory Distress Syndrome

14

Bairbre McNicholas, Emanuele Rezoagli, and John G. Laffey

14.1 AHRF and ARDS: A Definition Problem

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung process, which leads to protein-rich non-hydrostatic pulmonary oedema, causes refractory hypoxaemia, increases lung 'stiffness', and impairs the ability of the lung to eliminate carbon dioxide (Table 14.1) [8]. The clinical criteria for ARDS have undergone several iterations since its formal description by Ashbaugh and Petty in 1967 [9]. The Murray Lung Injury score in 1988 proposed a scoring system based on a number of quadrants affected on chest X-ray, degree of hypoxaemia, PEEP, and compliance [10]. This was superseded by the 1994 American European Consensus Conference definition [11], while the current working definition is the 'Berlin definition' [7]. Changes incorporated into the Berlin definition of ARDS include the

B. McNicholas
School of Medicine, National University of Ireland, Galway, Ireland

Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Saolta University Hospital Group, Galway, Ireland

E. Rezoagli
School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy

J. G. Laffey (✉)
School of Medicine, National University of Ireland, Galway, Ireland

Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Saolta University Hospital Group, Galway, Ireland

Lung Biology Group, Regenerative Medicine Institute (REMEDI), CÚRAM Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland
e-mail: john.laffey@nuigalway.ie

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Table 14.1 Characteristics of AHRF according to large clinical studies published in the literature and ARDS according to the Berlin's criteria

	AHRF					
Characteristics	Lewandowski AJRCCM 1995 [1]	The ARF Study Group AJRCCM 1999 [2]	FLORALI study group and REVA network NEJM 2015 [3]	PROVENT Lancet Respir Med 2016 [4]	LUNG SAFE JAMA 2016 [5]/Eur Resp Journal 2021 [6]	Berlin's criteria [7]
Timing	Not defined	'Acute' onset[a] in ALI/ARDS patients	Not defined	Not defined	Not defined	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Number of quadrants on the chest X-ray in which alveolar consolidations were observed (0–4)[b]	Bilateral infiltrates seen on a frontal chest radiograph (CXR)[a] in ALI/ARDS patients	Not defined	Not defined	Unilateral or bilateral new pulmonary parenchymal abnormalities on CXR or CT[c]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodule
Origin of oedema	Not defined	Pulmonary artery wedge pressure <18 mm Hg or no clinical evidence of left atrial hypertension[a] in ALI/ARDS patients	Absence of cardiogenic pulmonary edema	Not defined	Not defined	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostaticedema if no risk factor present

	AHRF					
Characteristics	Lewandowski AJRCCM 1995 [1]	The ARF Study Group AJRCCM 1999 [2]	FLORALI study group and REVA network NEJM 2015 [3]	PROVENT Lancet Respir Med 2016 [4]	LUNG SAFE JAMA 2016 [5]/Eur Resp Journal 2021 [6]	Berlin's criteria [7]
Oxygenation	Not defined	PaO_2/FIO_2 ≤ 300 mm Hg for ALI and PaO_2/FIO_2 ≤ 200 mm Hg for ARDS[a]	PaO_2/FiO_2 ≤ 300 mm Hg	Not defined	Ratio of arterial oxygen Tension to inspired fraction of oxygen (PaO_2/FIO_2) of 300 mmHg or less[c]	Mild ARDS: 200 mmHg <PaO_2/FIO_2 ≥ 300 mmHg Moderate ARDS: 100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg Severe ARDS: PaO_2/FIO_2 ≤ 100 mm Hg
Respiratory support	Intubation and mechanical ventilation ≥24 h regardless FiO_2 levels.	Intubation and mechanical ventilation ≥24 h regardless FiO_2 levels	Oxygen at a flow rate of 10 L per minute or more for at least 15 min	Invasive mechanical ventilation	Ventilatory support with continuous positive airway pressure (CPAP), expiratory positive airway pressure (EPAP), or positive end-expiratory pressure (PEEP) of 5 cm H_2O or more[c]	Mild ARDS: With PEEP or CPAP≥5 cm H_2O Moderate ARDS: With PEEP≥5 cm H_2O Severe ARDS: With PEEP≥5 cm H_2O
Respiratory rate	Not defined	Not defined	>25 breaths/min	Not defined	Not defined	Not defined

(continued)

Table 14.1 (continued)

	AHRF					
Characteristics	Lewandowski AJRCCM 1995 [1]	The ARF Study Group AJRCCM 1999 [2]	FLORALI study group and REVA network NEJM 2015 [3]	PROVENT Lancet Respir Med 2016 [4]	LUNG SAFE JAMA 2016 [5]/Eur Resp Journal 2021 [6]	Berlin's criteria [7]
$PaCO_2$ levels	Not defined	Not defined	$PaCO_2 \leq 45$ mm Hg	Not defined	Not defined	Not defined
Risk factor	Not defined	Not defined	Absence of: Clinical history of underlying chronic respiratory failure; exacerbation of asthma or chronic respiratory failure; cardiogenic pulmonary oedema; severe neutropenia; hemodynamic instability; use of vasopressors; a GCS ≤ 12; contraindications to noninvasive ventilation; urgent need for endotracheal intubation; a do-not-intubate order; and a decision not to participate.	Not defined	Not defined	Not defined

[a]Taken from the AECC Criteria for ALI/ARDS
[b]Taken from Murray Lung Injury Score
[c]Taken from the Berlin Criteria for ARDS

inclusion of non-invasive ventilation, clarification of the term 'acute', and the process for exclusion of cardiac failure as a cause [12]. More recent adaptations include the use of SpO_2 to facilitate ARDS diagnosis in resource-limited settings, and the use of lung ultrasound [13, 14]. While the 'classic' pathological lesion is diffuse alveolar damage, only a minority of patients fulfilling ARDS criteria at time of death demonstrate this lesion at autopsy, underlining the lack of specificity of current ARDS criteria [15].

The other pulmonary causes of Acute Hypoxaemic Respiratory Failure (AHRF) are grouped together into a poorly-defined entity characterized by an acute onset of hypoxaemia of pulmonary origin with unilateral infiltrates on imaging [7]. Given that the key distinguishing feature between ARDS and other cause AHRF is the absence of bilateral infiltrates on chest imaging in the latter condition, we will use the term unilateral-infiltrate AHRF (uAHRF) to describe them (Fig. 14.1). There is no standard definition of uAHRF with studies incorporating patients with varying criteria for respiratory support (oxygen therapy to invasive MV), oxygenation criteria (none, $PaO_2/FiO_2 < 300$ mm Hg), radiologic criteria (none, new infiltrates) and duration (none, 24 h, 1 week), and need for positive end-expiratory pressure support (none, ≥ 5 cm H_2O) [2, 12]. (Table 14.1) The lack of a single agreed set of diagnostic criteria constitutes a major impediment.

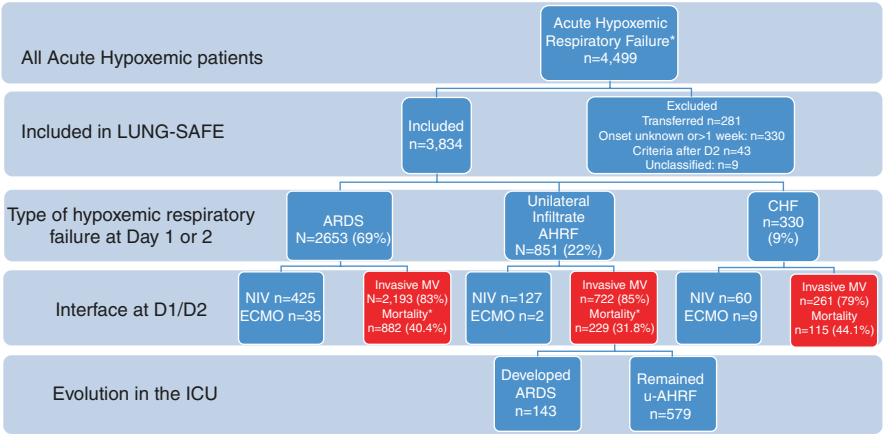

Fig. 14.1 Distribution and outcomes of patients with AHRF in the LUNG SAFE cohort. AHRF was defined by the following criteria: (**a**) $PaO_2/FIO_2 \leq 300$ mm Hg; (**b**) new pulmonary infiltrates on chest imaging; and (**c**) requirement of ventilator support with a positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O. Patients were divided into 3 groups: (**a**) ARDS, i.e., fulfilling all Berlin criteria for ARDS; (**b**) Congestive Heart Failure (CHF) patients in whom respiratory failure was considered by clinicians to be fully explained by cardiac failure or fluid overload; and (**c**) Unilateral infiltrate AHRF: patients fulfilling Berlin definition for ARDS criteria except that they presented with only unilateral infiltrates on chest imaging. *uAHRF* unilateral-infiltrate aHRF, *ARDS* acute respiratory distress syndrome, *CHF* congestive heart failure, *ECMO* extracorporeal membrane oxygenation, *NIV* non-invasive ventilation. Adapted with permission from Fig. 14.1 Pham et al. Eur Resp Journal [6]

Although there are overlaps between uAHRF, particularly when one compares 'focal' ARDS to uAHRF [2, 6], uAHRF constitutes a distinct entity, underlined by the fact that only a minority of patients progress to develop ARDS [6]. Optimizing the management of acutely hypoxaemic patients with unilateral infiltrates is important, given the limits of sensitivity of the current definition and the under-recognition of ARDS [16]. Additionally, adoption of 'lung protective' ventilation strategies in AHRF may be suboptimal, [17] particularly where the underlying lung mechanics differ significantly from that seen in ARDS.

A patient group that does not fit into the ARDS or the uAHRF classification is the rapidly growing group of acutely hypoxaemic patients receiving high flow nasal cannula (HFNC) oxygen therapy, as this involves end-expiratory positive pressures that are less than 5 cm H_2O.

14.2 Epidemiology: Knowns and Unknowns

Epidemiological studies have considerably advanced our understanding of the incidence, management, and outcomes of ARDS. Until recently, these studies were confined to localized regions and countries thereby offering widely differing estimates of the incidence of AHRF and ARDS [18]. However, more recent larger multinational collaborative studies, have cast doubt on the presence of major geographical differences in ARDS/uAHRF incidence. The LUNG SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE) study determined the incidence of ARDS and uAHRF using directly obtained clinical information rather than requiring physician recognition of ARDS [5]. It found that 10% of all patients in ICU, and 24% mechanically ventilated patients, fulfilled criteria for ARDS, while uAHRF of a sufficient severity to warrant non-invasive or invasive ventilation occurred in 4% of ICU patients (Fig. 14.1). Under-recognition of ARDS was a major issue, with only 30% of ARDS recognized at day 1 and 60% of ARDS recognized at any time, while geographic variation in ARDS incidence limited. LUNG SAFE also reported a mortality rate of 40% in patients with ARDS, casting doubt on data from randomized controlled trials suggesting decreased ARDS mortality over time [18].

There is greater heterogeneity in studies investigating the epidemiology of uAHRF compared to ARDS consistent with the lack of an accepted definition (Table 14.1) [1, 2, 4, 19–21]. Most recently, the PRoVENT study provided a similar global assessment of the epidemiology of AHRF. In patients without ARDS at onset of mechanical ventilation, 30% were deemed at risk for ARDS as defined by a lung injury prediction score >4 yet only 7% of these patients actually developed ARDS in the follow-up period compared with 3% in the group deemed not at risk for ARDS. Patients with undergoing invasive mechanical ventilation at risk for ARDS had a greater number of infections, pulmonary complications and longer ICU length of stay compared to patients deemed not at risk for ARDS.

14.3 Pathophysiology: Insights and Gaps

The 'classic' pathophysiological features of ARDS result from the widespread loss of alveolar function due alveolar consolidation and permeability derived pulmonary oedema leading to collapse of dependent areas of the lung. As a result, the lung compliance is generally—but not always—severely reduced, alveolar shunt and deadspace are high, while airway resistance is generally well preserved. Variations in this 'classic' ARDS pathophysiology are seen depending on features such as the distribution of lung infiltrates (i.e., focal versus diffuse), whether the underlying aetiologic risk factors are pulmonary versus extrapulmonary. These latter two entities frequently differ in terms of pathology with a more pronounced alveolar collapse, fibrinous exudative material, oedema of the alveolar walls and an increased collagen content described in pulmonary vserus extrapulmonary ARDS [22]. Insights in the complex interaction between alveolar epithelium, endothelium, coagulation, and immune system have been highlighted by presentations of ARDS induced by vitamin E acetate from vaping constituents and COVID-19 pandemic [23].

Recent advances in lung imaging and the biology of patients with ARDS allowed to better define ARDS based on (a) lung imaging criteria (i.e., focal versus non-focal or diffuse) that associate to a different ability to clear alveolar fluid and that differently correlate with outcome [24] and (b) the presence of inflammatory biomarkers (i.e., hyperinflammatory phenotype 2 versus phenotype 1) that differently associate to treatment (i.e., fluid and PEEP strategies) and outcome [25]. Computed-tomography (CT) studies led to the realization that a 'stiff' no-compliant lung is frequently really a small lung—the 'baby lung'—due to alveolar consolidation, oedema, and collapse [26]. Furthermore, CT studies obtained in ARDS patients in prone position allowed to visualize the inflamed lung as a functional sponge [27]. PET studies using 18F-D-glucose have demonstrated inflammation of parenchyma in both non-ventilated and apparently 'normal' ventilated lung regions [28].

As uAHRF encompasses a more diverse array of causative conditions causing acute severe hypoxia with a unilateral chest infiltrate on imaging, an even greater variability of pathophysiological patterns may be seen. One pathophysiologic feature may predominate, such as shunt (e.g. bronchopneumonia), increased airways resistance (e.g. acute exacerbation of Asthma), reduced elastic recoil with dynamic hyperinflation (Asthma, COPD). Importantly, pathophysiologic features that predominate in ARDS, such as low lung compliance, are less frequently encountered, which may have important implications for ventilatory management.

14.4 Support of Gas Exchange

The use of HFNC oxygen to restore oxygenation and reduce work of breathing has increased substantially in recent years, particularly during the COVID-19 pandemic. Its use is supported by a growing evidence base, and is increasingly

considered the first level of 'advanced respiratory support' modalities for both uAHRF and ARDS patients [20, 29]. Non-invasive ventilation strategies (NIV) have an established evidence base in the management of AHRF causes such as acute exacerbations of COPD and asthma, and in pneumonia [12]. Differences in response to NIV and HFNC may exist depending on the subtype of AHRF, with HFNC superior to NIV in AHRF [20] while NIV reduced in need for IMV, while HFNC was ineffective, in a study of patients with COVID-19 induced AHRF [30].

The role of NIV in ARDS is more contentious given the potential for 'self-induced lung injury' in the presence of an increased respiratory drive [31]. In the LUNG SAFE cohort, mortality was lowest in ARDS patients who were successfully managed on NIV [12]. However, over a third of patients failed NIV, and mortality in this cohort was 45%. In a propensity matched analysis, mortality was increased in ARDS patients with P/F ratio <150 compared to similar patients managed with invasive MV. [12]. In patients who failed NIV, institution of invasive MV led to a substantial reduction in tidal and minute ventilation. This raises concerns regarding persisting with NIV in patients who are not responding, with failure to implement earlier lung protective ventilation in this cohort. [12] Similar findings were also reported in an AHRF cohort, where patients in whom NIV did not reduce work of breathing and improve oxygenation within 1 h of starting NIV were four times more likely to require invasive MV [3]. These findings underline the need to assess the response to NIV at regular intervals following commencement, irrespective of the cause of AHRF.

Personalizing and appropriately selecting patients for NIV is critical for its best use in ARDS and AHRF. Prognostication scores such as the HACAR or ROX index may identify patients who are responding or who are likely to fail non-invasive therapies [32, 33].

14.5 Invasive Mechanical Ventilation: From 'Protective' to 'Personalized'

Invasive MV is lifesaving in patients failing other forms of advanced respiratory support, it can worsen ARDS severity, with high tidal volumes increasing shear stress in stiff lungs, causing volutrauma, barotrauma, and biotrauma [34]. Lung ventilation strategies that limit tidal volume to 6–8 mls/Kg predicted body weight and plateau pressures below 30 cm H_2O increase patient survival in ARDS [35]. However, the approach to optimizing the settings for other ventilation parameters, such as oxygen titration (conservative versus liberal), PEEP (lower versus higher), and lung recruitment strategies (open versus closed lung) in ARDS patients are less clear. Future progress with optimization of ventilation in ARDS patients may include developing strategies to individualise ventilator settings at the bedside [36, 37]. In regard to optimal setting of PEEP, the response in terms

of oxygenation and/or lung compliance to an upward PEEP titration appears to hold promise [38]. The potential for 'personalized' ventilation in ARDS is highlighted in the LIVE study, patients were randomized to two ventilation strategies based on whether they had focal versus diffuse ARDS infiltrates versus a control group receiving a standardized 'protective ventilation' approach [17]. While no outcome difference was seen in the primary analysis, there was a high rate of misclassification which when reclassified, resulted in a benefit in the personalized ventilation arm [17]. These data suggest the need to titrate lung ventilation parameters to the underlying lung physiology, rather than adopting 'one size fits all' ventilation strategy [39]. Accordingly, the use of dynamic indices such as driving pressure to guide titration of tidal volume at the bedside has gained widespread popularity in recent years [40].

The optimal approach to invasive MV in patients with uAHRF is even less well understood, as the evidence base here is limited. While high tidal volume ventilation is injurious even in previously normal lungs, [4, 41] and should clearly be avoided in uAHRF patients, the best approach to titrate tidal volume in this group is not known. There may be no additional advantage to very low tidal volumes in patient with uAHRF, and the accompanying measures required to ensure patient tolerance for these approaches (e.g. sedation) especially where compliance is maintained. Indeed, even in the ARMA study, patients with ARDS in the highest quartile of lung compliance had no mortality benefit from the ARDSnet lung protective strategy [35].

14.6 Adjuncts to Ventilation

Prone positioning of invasively ventilated patients with confirmed moderate to severe ARDS is supported by a clear evidence base [42] and represents standard of care. Despite this, the use of prone positioning remains low in this patient cohort. [5] A recent innovation during the COVID pandemic has been extending prone positioning to awake patients receiving non-invasive respiratory support, which has been demonstrated in a large meta-trial to reduce the need for invasive ventilation [43]. The role of awake prone positioning in non-COVID patient with uAHRF or ARDS, and the role of prone positioning in invasively ventilated uAHRF patients remain to be determined.

The use of neuromuscular blockade in patients with moderate to severe ARDS is supported by some [44] but not all studies, [45] although differences in methodology may explain the divergent findings. There is no data available regarding the use of muscle relaxants in uAHRF.

Data from observational studies suggest a wide variety of practice in adjunct use in ARDS, with the recent SAGE study finding frequent use of systemic steroids (41.5% vs 19.4%) and neuromuscular blockade (27.4% vs 25.6%), but low rates of prone positioning (5.8% vs 7.9%), the adjunctive therapy that has most clearly

demonstrated benefit in moderate to severe ARDS [46]. Underuse of key evidence based treatments has been noted in other studied suggesting practitioners individualizing based on experience rather than tailoring to patient's needs [47, 48].

14.7 Specific Therapies for ARDS and AHRF

There are no specific pharmacological treatments for ARDS despite over 50 years of research and many negative clinical trials [49]. Pharmacological strategies for uAHRF focus on management of the underlying condition, and there is a dearth of pharmacologic trials in this population.

One recent trial of dexamethasone in established moderate–severe ARDS [50], while the demonstration that dexamethasone reduced mortality and progression of COVID-19 AHRF suggests that steroid therapy may have been discarded prematurely [51]. An evidence base is developing for the concept that therapies may need to be targeted at specific subphenotypes, such as patients with a 'hyperinflammatory' response. Calfee and colleagues, in a reanalysis of the HARP trial of simvastatin for ARDS, found that patients with a hyperinflammatory subphenotype appeared to benefit from simvastatin therapy [52]. These findings underline the importance of developing real-time population enrichment strategies that can then be targeted in the future clinical trials [53].

14.8 Outcomes

Data from LUNG SAFE highlighted that patients with ARDS continue to have a high mortality with 40% of patients dying in hospital, despite advances in supportive care (Fig. 14.1) [5]. More recently, a similar mortality rate of 40.7% was confirmed in the American SAGE study that included patients with moderate–severe ARDS. One aspect of ARDS is deciphering the actual morbidity and mortality directly attributable to ARDS [54, 55]. In a post-hoc analysis of two studies of sepsis (EARLI and VALID), an attributable mortality for severe ARDS of 16–18% was reported, with the mortality risk plateauing at a PFR of 120. This compares to an attributable fraction of mortality of 11% and 7% for ICU acquired infection and delirium, respectively [56].

The outcome for AHRF has been understudied compared to that of ARDS. A Scandinavian study in the 1990s found a mortality of 40% for both ARDS and non-ARDS related ARF [2]. In the LUNG SAFE study, patients with ARDS requiring invasive ventilation had an unadjusted hospital mortality of 40% compared to 32% for uAHRF, [6] supporting the concept that ARDS may confer an additional mortality risk [6]. However, when uAHRF patients with infiltrates in 2 unilateral quadrants were compared to AHRF patients with 2 quadrant infiltrates, there was no difference in mortality rates. In multivariate analyses, the number of lung quadrants affected, rather than the distribution of the quadrants (unilateral versus bilateral) was the key contributor to mortality risk (Fig. 14.2) [6].

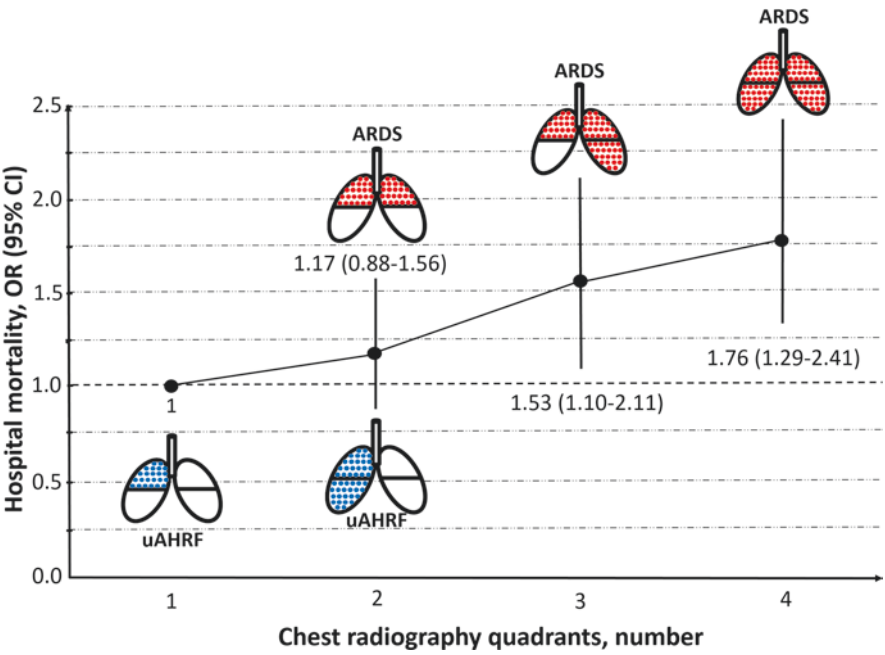

Fig. 14.2 Adjusted risk of hospital death in patients with AHRF in the LUNG SAFE cohort. Patients with respiratory failure may present unilateral infiltrates—AHRF (blue dots) or bilateral infiltrates—ARDS (red dots). The presence of infiltrates in 2 quadrants can overlap AHRF or ARDS based on their unilateral or bilateral distribution, respectively. The increasing number of quadrants with lung infiltrates (i.e., above 2) was associated to a progressively increasing risk of death compared to the presence of only one quadrant involved with infiltrates. The Odds ratio with 95% confidence interval was adjusted for baseline characteristics, comorbidities, presence of concomitant cardiac failure, risk factors of ARDS, ventilatory variables, and geoeconomic variations. Odds ratio and 95% CI were represented by dots and error lines. One quadrant was used as reference. Note: Graphic representation of Data from Pham et al. Eur Resp Journal [6]

14.9 AHRF: Changing the Paradigm

The lack of an agreed set of diagnostic criteria constitutes a major impediment to advancing our understanding and improving the outcomes of patients with AHRF. Research effort to date has largely concentrated on ARDS, leading to an under-appreciation of the burden of uAHRF. A unifying definition of AHRF is urgently required. A standard definition, adapted from the existing Berlin criteria for ARDS, and which could be easily operationalized could include the following criteria: (a) onset <1 week; (b) hypoxaemia with P/F ratio <300 mm Hg; (c) need for advanced respiratory support (i.e., ≥40 L/min high flow nasal cannula oxygen); (d) radiologic evidence of new pulmonary infiltrates; and (e) absence of cardiogenic cause as primary reason for hypoxaemia. The subset of patients with ARDS would then be distinguished solely on the presence of bilateral infiltrates on chest imaging.

AHRF and ARDS severity would be graded based on current P/F ratio categories, while consideration could also be given to number of quadrants affected on chest radiology. Further refinements of the ARDS definition could be incorporated, including differentiation of subphenotypes on the extent of lung involvement (lung quadrants; focal versus diffuse distribution), respiratory mechanics profiles, or panels of biomarkers assessing inflammation and lung epithelial and endothelial injury [52, 57].

This new unified set of diagnostic criteria could be implemented into electronic medical record systems, and may enhance recognition of ARHF and ARDS, prompting careful tailoring of respiratory support strategies to the underlying physiology. These definitions should also form the basis for future research efforts. These should focus on understanding the epidemiology of the different causes of AHRF, to fully understand the disease burden and outcomes from AHRF. Interventional studies could then test respiratory support strategies in different AHRF subtypes, potentially facilitate identification of AHRF subsets based on treatable traits, whether physiologic (e.g., PEEP responsiveness; prone positioning) or biologic (e.g., steroid responsiveness).

14.10 Conclusions

AHRF is induced by a diverse set of clinical conditions, and when it requires critical care management, it results in a mortality of 40%. Mortality appears to be influenced more by the extent of lung involvement, as reflected by the number of lung quadrants affected, rather than whether ARDS is present or not. The lack of an agreed set of diagnostic criteria for AHRF constitutes a major impediment to advancing care and improving outcomes in these patients and should be addressed as a matter of urgency. There is a clear need to fully understand the disease burden of AHRF induced by entities other than ARDS, and to develop an evidence base for management and treatment strategies in these patients. An integrated set of criteria that includes ARDS and other pulmonary causes of ARDS should be easy to operationalize and facilitate the early recognition of these conditions thereby allowing individualization of management and reduction of iatrogenic injury. At a global level, understanding the burden of AHRF will allow policy makers to plan and equip ICUs with appropriate staffing, equipment, and conduct follow-up studies on the long-term effects [58]. Ultimately, this approach should lead to the development of novel specific therapies and tailored support approaches for AHRF patients leading to improved outcomes for these patients.

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Ventilator-Induced Lung Injury and Lung Protective Ventilation

15

Guillermo M. Albaiceta and Laura Amado-Rodríguez

Mechanical ventilation is an essential supportive therapy for patients with respiratory failure: it may improve gas exchange, decrease work of breathing, and ensure ventilation in patients unable to do so. However, high airway pressures trigger a variety of responses in the respiratory system, that in some cases can be detrimental and lead to the onset or worsening of lung damage, termed Ventilation-Induced Lung Injury (VILI) [1].

Positive-pressure ventilation has been suggested to be harmful long before modern mechanical ventilators were developed. As early as 1744, British physician John Fothergill speculated that mouth-to-mouth resuscitation could be a less injurious option than using a bellow when trying to restore "the apparently dead" [2]. His mind was focused on the mechanical load supported by the lungs after insufflating

G. M. Albaiceta (✉)
Unidad de Cuidados Intensivos Cardiológicos, Hospital Universitario Central de Asturias, Oviedo, Spain

Departamento de Biología Funcional, Instituto Universitario de Oncología del Principado de Asturias. Universidad de Oviedo, Oviedo, Spain

Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain

Centro de Investigación Biomédica en Red-Enfermedades Respiratorias, Madrid, Spain
e-mail: guillermo.muniz@sespa.es

L. Amado-Rodríguez
Unidad de Cuidados Intensivos Cardiológicos, Hospital Universitario Central de Asturias, Oviedo, Spain

Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain

Centro de Investigación Biomédica en Red-Enfermedades Respiratorias, Madrid, Spain

Departamento de Medicina, Instituto Universitario de Oncología del Principado de Asturias, Universidad de Oviedo, Oviedo, Spain

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gas proceeding from a bellow or from another person's airway, the volume generated by the former being presumably larger.

Avoidance of VILI is a major goal in critically ill patients and has been related to improvements in survival. In this chapter, we will review the mechanisms by which mechanical ventilation may cause lung damage, their bedside assessment and the evidence favoring the so-called protective ventilatory strategies in the clinical practice.

15.1 Mechanosensitivity of the Respiratory System

Most cells are mechanosensitive, as they sense and react to mechanical stimuli. This is especially relevant in tissues submitted to continuous or cyclic forces, such as the respiratory system. There is a large variety of cell mechanosensors, including stretch-activated ion channels in the plasma membrane (i.e., Piezo and TRPV families), cell cytoskeleton or the nuclear envelope itself. Activation of these sensors triggers cell reprogramming and induces changes in gene expression.

Under physiological conditions, ventilatory drive regulates frequency, amplitude, and pattern of ventilation in response to several feedback mechanisms such as blood gases or airway stretch, thus determining the magnitude of the mechanical load self-imposed on the respiratory system [3]. In the respiratory epithelium, tidal stretch activates cell proliferation/migration and surfactant secretion. Excessive or sustained activation of these mechanodependent pathways may result in pathogenetic responses. Among these, inflammation, regulation of cell survival, and extracellular matrix remodeling play a central role in VILI (Fig. 15.1).

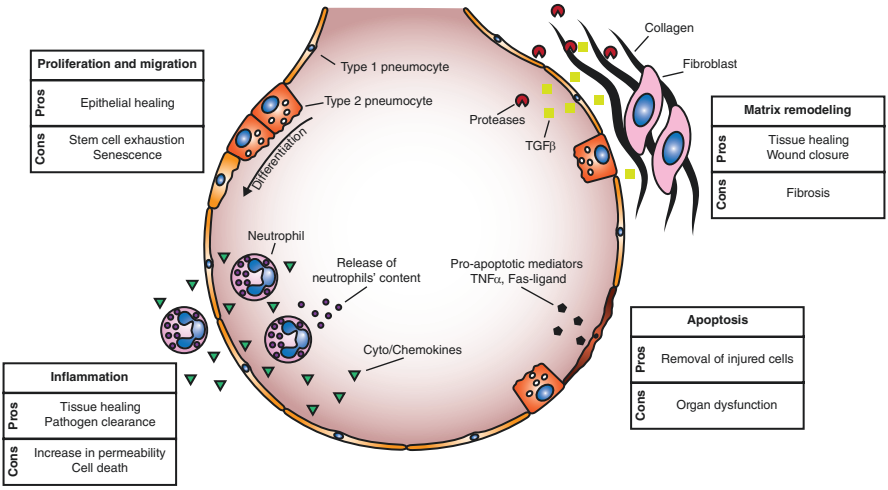

Fig. 15.1 Biological responses to mechanical stretch involved in Ventilator-induced lung Injury. All these mechanisms have both pro-repair (PROS) and pathogenetic effects (CONS), depicted in the figure

Mechanical stretch per se may induce the release of proinflammatory molecules from the alveolar epithelium. The generated chemokine gradient recruits neutrophils from the circulation. Activated neutrophils release their granules (containing proteases, reactive oxygen species, and inflammatory mediators) within the alveolar space and interstitium, causing tissue disruption [4]. The loss of the epithelial barrier integrity facilitates the translocation of these mediators from the alveoli to the circulation and vice versa [5]. Notably, some of the released molecules, such as interleukin-1β or − 6 act also as growth factors that contribute to tissue repair [6].

Mechanical stimuli modulate cell survival through a variety of intracellular mechanisms. Stretch per se may stimulate cell division and differentiation, thus facilitating epithelial repair [7]. However, excessive activation of mechanical receptors can trigger cell cycle arrest and/or apoptosis [8]. Although apoptosis constitutes a mechanism to remove damaged cells without causing significant inflammation, the massive loss of cells in response to high stretch can cause tissue dysfunction.

Finally, mechanical stretch results in the activation of matrix remodeling pathways that include matrix synthesis, processing, and degradation [9]. Several inflammatory mediators, such as TGFβ, activate collagen synthesis and deposition. Stretch promotes the release of proteases (elastase, matrix metalloproteinases), either from alveolar or recruited inflammatory cells, that can cleave not only components of the extracellular matrix, but also other molecules such as cyto- and chemokines. In the acute phase, proteases are responsible for alveolar destruction, so that their inhibition may prevent VILI. However, there is an increasing evidence on their role on later repair by collagen and cytokine processing [10].

All these pathogenetic mechanisms must be viewed as the extreme of a physiological response aimed to preserve the integrity of the respiratory system. This dual nature of the responses to stretch (illustrated in Fig. 15.1) may explain the failure of most therapies against VILI in the clinical setting, as most of them may impair lung function in the short term but are required for efficient tissue repair/regeneration. To be effective, an intervention must not only target a relevant pathway, but also in a specific timing that avoids interference with the intrinsic tissue repair mechanisms.

15.2 Pathophysiology of Ventilator-Induced Lung Injury

Mechanosensation is a local phenomenon. This means that only regional stretch or pressure, but not global lung volume, are sensed. In healthy lungs, air is homogeneously distributed. Although basal and non-dependent areas receive larger gas volumes due to their higher regional compliance, gas is evenly distributed in neighbor alveoli and acini. For these reasons, normally aerated, non-injured lungs may be resistant to VILI. In a homogeneous parenchyma, only tidal volumes (V_T) high enough to cause regional overdistension and increase transpulmonary pressure even after distribution along the whole lung may cause damage. The measurement of

functional residual capacity (FRC) has been proposed as a marker of the amount of tissue available for ventilation [11, 12], so that VILI appears only when the ratio of V_T/FRC (the strain of the respiratory system) increase above a certain threshold (around 1.5). The effectiveness of the stability mechanisms to ensure homogenous distribution of forces within the respiratory system explains the tolerance to V_Ts well above 6 ml/kg (the normal V_T in most healthy mammals) without causing injury in patients with normal lungs.

The clinical relevance of VILI emerges with a heterogeneous distribution of the inspired gas and/or the distending forces. There are several factors that predispose to VILI in previously injured lungs:

1. Lungs exposed to a *proinflammatory environment* are more susceptible to VILI, given the synergistic effect of systemic inflammation and injurious ventilation [13]. However, the relevance of this mechanism in patients without lung injury are less clear.
2. An *inhomogeneous distribution of the inspired gas* due to regional differences in tissue compliance may cause regional alveolar overstretching. When a large number of alveoli are not available for ventilation (due to alveolar collapse, occupation, or very low regional compliance), the bulk of V_T will be diverted to the aerated zones (the "baby lung"). This is the rationale for proposing the use of V_T according to the amount of aerated lung [14]. The consequence of using inappropriately large volumes is regional overdistension. In patients with the acute respiratory distress syndrome (ARDS), non-dependent and apical areas are usually aerated due to the absence of gravitational forces that promote collapse, and thus exposed to overstretching [15].
3. The *coexistence of air–tissue interfaces* causes an anisotropic distribution of forces along the tissue structure, amplifying their magnitude. Regional pressures increase in septa between aerated and non-aerated alveoli by a factor defined by the ratio between alveolar volumes to a power of 2/3 (so that, in poorly aerated areas, an airway pressure of 30 cm H_2O may be locally amplified up to 120 cm H_2O) [16].
4. An abnormal air distribution and the failure of mechanisms responsible for preservation of end-expiratory volume (i.e., surfactant depletion, instable chest wall…) may promote *large variations of alveolar size* along the respiratory cycle (termed alveolar instability) and end-expiratory collapse. These large changes in aeration increase the mechanical load over the alveolar/airway cells [16].

All these mechanisms converge in an abnormally increased stretch and pressure over alveolar cells, triggering the previously described biochemical responses that perpetuate lung damage. From a clinical point of view, all these mechanisms have been grouped, and probably mixed, under the terms barotrauma, volutrauma, atelectrauma, and biotrauma. Table 15.1 defines these concepts and their implications for clinical management, that will be discussed in the following sections.

Table 15.1 Classic mechanisms of ventilator-induced lung injury

Term	Definition
Barotrauma	Damage caused by elevated transpulmonary pressures, causing from large air leaks to alveolar injury
Volutrauma	Damage caused by alveolar overdistension
Atelectrauma	Damage caused by tidal changes in aeration, either by repeated aeration/collapse cycles or large deformation of the alveolar structure
Biotrauma	Release of inflammatory mediators and other molecules triggered by ventilator-induced lung injury to the circulation

15.3 Bedside Assessment of VILI

The coexistence of VILI with other forms of lung injury makes the identification and monitoring of the former a difficult task in the clinical setting. Since VILI causes a stereotypical lung response, it is nearly impossible to differentiate the amount of damage caused by ventilation from the underlying disease in previously injured lungs. By these reasons, the concept of VILI has been translated to patients as Ventilator-associated lung injury (VALI) [17].

Being a phenomenon initiated by an excessive mechanical load, there is substantial interest on the use of respiratory mechanics to monitor VILI/VALI. Plateau pressures represent end-inspiratory alveolar pressure and, given their ease to be measured, are widely used. It has been suggested that P_{plat} should be kept below 28–30 cm H_2O [18]. However, in patients with impaired chest wall mechanics or spontaneous breathing, plateau pressures can be misleading. In these cases, esophageal pressure monitoring allows to estimate pleural pressure and calculate transpulmonary pressure, the true distending pressure applied on lung parenchyma. An end-inspiratory transpulmonary pressure below 20–25 cm H_2O and an end-expiratory transpulmonary pressure above 0 have been recommended to avoid overdistension and end-expiratory collapse, respectively [11].

Driving pressure (plateau pressure minus PEEP) reflects the relation between the applied V_T over a given PEEP and respiratory system compliance, and has emerged as a better marker of injurious ventilation due to its relationship with the cyclic phenomena behind VILI. A driving pressure threshold of 15 cm H_2O has been related to better outcomes in ARDS [19]. Respiratory system or lung compliance may vary with different respiratory settings. However, outside extreme cases (such a massive decrease in compliance due to very high V_T or PEEP levels, suggesting overdistension), the coexistence of several phenomena (including tidal recruitment, alveolar overdistension or increase in end-expiratory lung volume) with opposed effects on the mechanisms of VILI makes compliance an unreliable marker of ongoing damage. The same reasoning can be applied to static pressure–volume curves [20]. Lung strain (defined as the ratio of V_T to FRC) or a surrogate using V_T to end-expiratory lung volume ratio have been tested in animal models and pathophysiological studies [11, 12, 21]. Although these measurements can help to identify a safe V_T by adjusting its value to the amount of aerated lung, no sound clinical evidence

has been provided. All these measurements based on respiratory mechanics render global values. However, as previously discussed, VILI is a local phenomenon enhanced by regional heterogeneity, so it may occur even in presence of normal "averaged" measurements of respiratory mechanics.

Imaging techniques may provide regional information required to identify areas exposed to different types of mechanical damage. Computed tomography has been widely used to describe lung response to mechanical ventilation. Using dynamic, quantitative CT techniques, cyclic changes in aeration and overdistension can be identified according to their radiologic density. These results have been correlated to circulating cytokines and ventilator-free days in ARDS patients [22]. However, these measurements are difficult to incorporate in the routine care of critically ill patients. Electrical impedance tomography, performed at the bedside, may solve some of these drawbacks [23]. Regional compliances, defined as the ratio of change in aeration to change in pressure, may be used to identify overdistension (as aerated areas with low compliance) and cyclic changes in aeration.

Finally, the possibility of a biological monitoring of VILI using biomarkers must be considered. Several molecules have been proposed as biomarkers of lung injury, including immune mediators (sRAGE, IL-6), proteins from the respiratory system (surfactant proteins, KL-6), growth factors, or complex combinations of genes and/or microRNAs quantified in peripheral blood [24]. However, none of these molecules have been identified as specific for VILI or any of its underlying mechanisms (i.e. alveolar stretch or cyclic collapse).

In summary, quantifying VILI at the bedside is a difficult task due to the absence of a gold standard, especially in patients with previous lung injury. The integration of respiratory mechanics and imaging techniques with the clinical picture and evolution may help the clinician to adjust the ventilator toward more protective settings.

15.4 Designing Lung Protective Strategies

Avoidance of VILI is a major goal in current critical care. Limitation of the mechanical load imposed by positive-pressure ventilation over the lung tissue is the best approach to avoid further damage. The concept of protective ventilation includes strategies aimed to achieve this goal of avoiding VILI, even at a price of worse gas exchange or the need for invasive procedures such as extracorporeal gas exchange.

Different ventilatory settings have multiple effects in the lung parenchyma, especially if there is a heterogeneous distribution of aeration. Most research has focused on positive end-expiratory pressure (PEEP) and V_T, but other settings such as respiratory rate or peak flow may also be relevant. Positive end-expiratory pressure increases end-expiratory lung volume by both inflation of previously aerated zones and recruitment of non-aerated or collapsed areas. Therefore, its effects on VILI mechanisms may vary from an increase in the amount of tissue available for ventilation (thus decreasing strain and favoring homogeneous ventilation) to overdistension of previously aerated alveoli [21] (see Chap. 17).

V_T adjustments are the cornerstone of VILI prevention. Healthy lungs, where the mechanisms of VILI are dampened, can tolerate moderate V_T without significant injury. However, in experimental models of lung injury, there is a continuous decrease in VILI with V_T decrements from 12 to 3 ml/kg [25]. There is substantial consensus that large V_T (arbitrarily defined as those above 8 ml/kg or causing increases in plateau or driving pressures above 28 and 15 cmH_2O, respectively) should be avoided in patients with lung injury, and a V_T of 6 ml/kg of predicted (rather than actual) body weight (estimated using height) has been proposed as a standard of care in ARDS patients [26, 27]. However, individual titration of V_T is still debated. The safety of larger V_T in ARDS cases with high compliance has been suggested but not tested in trials [28]. More important, currently available devices for extracorporeal gas exchange allow CO_2 washout and subsequent reductions in V_T. Ultralow V_T may prevent end-inspiratory overdistension and cyclic changes in aeration, but also promote lung collapse due to the loss of end-inspiratory recruitment [29]. Collectively, although guidelines propose values around 6 ml/kg in ARDS patients, fine tuning of V_T is still an unsolved issue and reflects the current limitations in VILI monitoring.

Other ventilatory settings may be adjusted to attenuate VILI. For a given inspiratory pressure, lower respiratory rates decrease mechanical load of the respiratory system and injury. High inspiratory flow has been associated also with lung injury, probably related to small airway damage. Clearly, V_T, respiratory rate and inspiratory flow are closely related, and cannot be set independently. The optimal solution for this interdependence is not clear, but experimental research suggests that the relevance of V_T in induction of VILI is higher than the other parameters [30].

Preservation of spontaneous breathing during mechanical ventilation may also influence the development of VILI. Contraction of inspiratory muscles generates higher local transpulmonary pressures in dependent areas, which remain poorly aerated during injury. Therefore, spontaneous breaths may help to recruit collapsed areas and render ventilation more homogeneous, contributing to decrease VILI. However, respiratory muscles can develop very high transpulmonary pressures (sometimes without raising, or even decreasing, plateau and driving pressures), and patient-ventilator asynchronies can lead to very high V_T (i.e., breath stacking). The risk of lung damage triggered by spontaneous breaths (with or without mechanical ventilation) has been termed "patient self-inflicted lung injury" (P-SILI). Although the relevance of P-SILI is controversial, it has been suggested that inspiratory efforts should be monitored and excessive transpulmonary pressures or asynchronies avoided at least during the early phases of acute lung injury [31].

Collectively, a lung protective ventilatory strategy should include a V_T that avoids end-inspiratory overdistension and a PEEP level that avoids end-expiratory loss of previously aerated zones, with respiratory rate and inspiratory flow adjusted at a minimum that ensures gas exchange and patient comfort. Adjustments of these parameters at the bedside must rely on respiratory mechanics and imaging techniques, but keeping the limitations of these monitoring techniques in mind (Fig. 15.2).

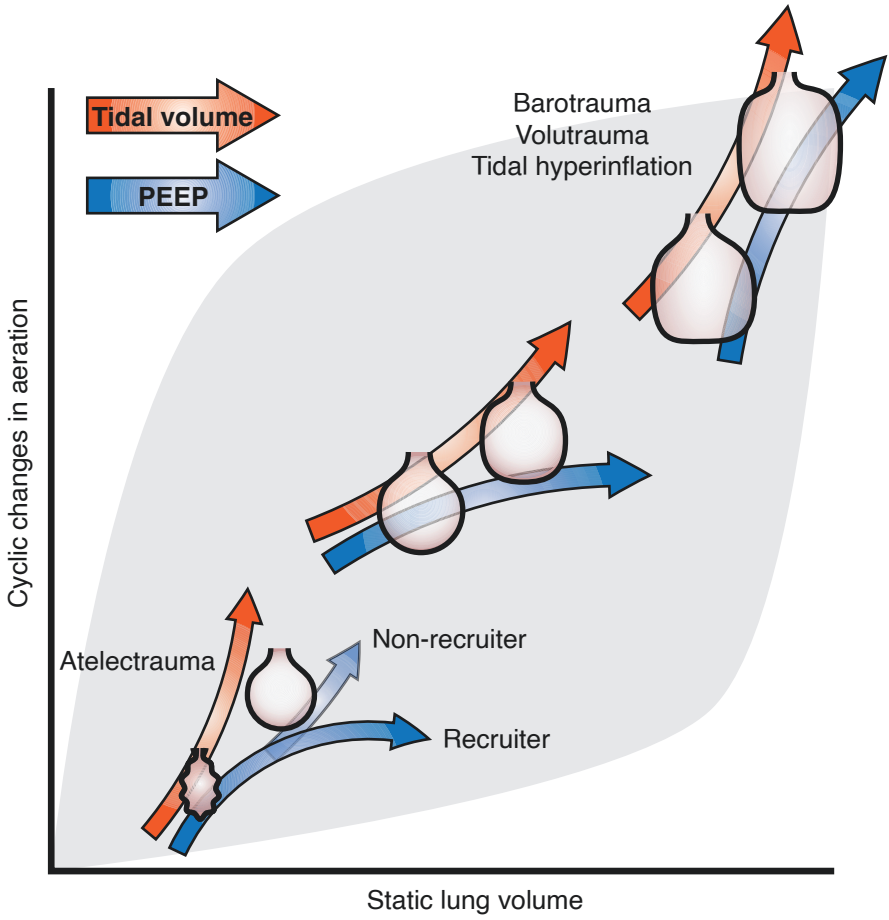

Fig. 15.2 Effects of tidal volume and PEEP. Pairs of alveoli represent end-expiratory and end-inspiratory conditions. In injured lungs, the effects of ventilatory settings on static lung volume and cyclic changes in aeration depend on the previous aeration and the nature of the injury. The so-called recruitable lungs may show a better response to PEEP, thus favoring the increase in static volumes and a decrease in cyclic changes in aeration

A completely different strategy should be the prevention of VILI by targeting the biological mechanotransduction machinery its downstream pathways involved in lung injury. In experimental models, a large variety of drugs and biological strategies decrease lung damage after injurious ventilation. However, none of these drugs has been successfully translated to the clinical practice [32]. The complexity of patients, as opposed to experimental models, and the dual nature of most of the cell response triggered by stretch (both homeostatic and pathogenetic) complicates the identification of an effective pharmacological treatment for VILI.

15.5 Clinical Evidence on Protective Ventilation

It took more than two centuries from the prophetic Fothergill's concerns to collect sufficient clinical evidence to support protective ventilatory strategies. Reducing V_T from 10 or 12 ml/kg of predicted body weight to 6 ml/kg is the only ventilatory strategy capable of reducing mortality in patients with ARDS to date. Although the seminal studies by Amato [27] and the ARDSnet Investigators [26] marked a milestone in critical care management, few years later, further analysis suggested that the survival benefit was related to the reduction in driving pressure rather than low V_T per se [19]. However, the potential benefit of setting V_T using driving pressure is yet to be demonstrated though appeared feasible in patients with the ARDS [33].

Far from being solved, concerns about the reliability of airway pressures were concomitantly raising, since alterations in chest wall elastance could translate different transpulmonary pressures for the same V_T. Clinical evidence regarding the benefit of using this parameter to adjust ventilation in patients with the ARDS is scarce. Use of esophageal pressure to adjust PEEP allowed to improve oxygenation and respiratory compliance [34], but failed to demonstrate benefit in patient-centered outcomes [35].

Following the reduction in mortality observed after a low V_T strategy, a natural trend to continue reducing the mechanical load led to the application of the so-called ultraprotective ventilatory strategies. In clinical settings, these strategies have been proven to be safe and feasible in the context of extracorporeal support [36]. While some studies suggest a reduction in lung inflammation [29, 37], no benefits in terms of mortality were demonstrated [38]. This lack of survival benefit precludes any recommendation for ultralow V_T ventilation application while do not exclude the possibility that potential benefit in selected high-risk populations.

Clinical evidence of VALI in patients without pre-existent pulmonary disease is scarce. In healthy lungs, even short periods of ventilation during surgical procedures can lead to a reduced functional residual capacity. Although a certain level of PEEP might reduce lung strain and approximate ventilatory settings to more protective parameters, a low PEEP-based strategy has been reported to be non-inferior when compared to higher PEEP levels in patients without ARDS [39]. Similarly, V_T in patients without ARDS have been related to variable results. A clinical trial comparing low and intermediate V_Ts in this population showed no differences in clinical outcomes between both strategies [39].

Collectively, clinical data shows that the impact of V_T is larger than any other ventilatory parameter, and enough to improve survival in unselected ARDS patients. In opposite, the failure of other ventilatory settings to demonstrate a clinical benefit suggest that their effect on VILI is minor or counterbalanced by side effects. In this scenario, the current challenge is to identify specific, enriched populations that could benefit from fine-tuning of one of these additional settings or further optimizations in V_T.

15.6 Conclusion

VILI can be seen as the lung response to exposure to abnormal mechanical forces. The biological responses in VILI recapitulate the lung standardized response to injury (include inflammation, apoptosis, and matrix remodeling). Currently, the only approach to ameliorate VILI is the use of protective ventilatory strategies, including low V_T (and probably low driving pressures) and moderate PEEP levels. The lack of gold standards for VILI monitoring makes adjustment of ventilation at the bedside a difficult task for clinicians. Clinical trials have shown that low V_Ts that result in low driving pressures decrease mortality in ARDS patients, while their role in patients without previous lung injury is controversial. Monitoring techniques that allow detection of ongoing mechanical lung damage and individualized titration of ventilatory settings and novel pharmacological approaches targeting the molecular mechanisms of VILI are warranted to improve the outcome of ventilated patients.

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Mechanical Ventilation in the Healthy Lung: OR and ICU

16

Fabienne D. Simonis, Frederique Paulus, and Marcus J. Schultz

16.1 Introduction

Over the past three decades, the medical literature has been enriched with seminal observational investigations and randomized clinical trials dealing with mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) [1]. The knowledge that emerged from these studies has changed the way we set ventilators in patients with ARDS. Interestingly, the findings of these studies have also been used to adjust ventilator management in patients with healthy lungs.

On the one hand, what is good for patients with ARDS could also be good for patients with healthy lungs, for instance, when it comes to the prevention of harm induced by mechanical ventilation—think here of reductions in the size of the tidal volume (V_T), which may prevent overdistension of lung tissue. On the other hand, certain strategies could have serious side effects, and maybe even more in patients with healthy lungs than in patients with ARDS—think here of increases in positive end-expiratory pressure (PEEP) that may or may not recruit lung tissue but at the price of alveolar overdistension and hemodynamic instability. We may also need to

F. D. Simonis (✉) · F. Paulus
Department of Intensive Care, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands
e-mail: f.paulus@amsterdamumc.nl

M. J. Schultz
Department of Intensive Care, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands

Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A), Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands

Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand

Nuffield Department of Medicine, University of Oxford, Oxford, UK

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acknowledge that extent of harm induced by mechanical ventilation in patients with healthy lungs could be less than in patients with ARDS—this could make certain ventilation strategies less effective, or even not effective at all in patients with healthy lungs. Last but not least, a patient that does not or not yet fulfills the current definition for ARDS could still have injured lungs or develop lung injury later on—thus we may need to adjust ventilator settings over time. Here we also need to hold in mind that critically ill patients, i.e., patients under mechanical ventilation in the intensive care unit (ICU), could differ in many ways from surgery patients, i.e., patients under intraoperative ventilation during general anesthesia for surgery in the operating room (OR)—think here of differences in the total duration of ventilation, much longer in critically ill patients, and presence of spontaneous breathing activity, much less often present in the anesthetized and usually paralyzed surgery patients.

In this chapter we discuss the current knowledge with regard to mechanical ventilation in patients with healthy lungs, in the OR in patients under intraoperative ventilation during general anesthesia for surgery, and in the ICU in critically ill patients without ARDS. We deliberately split the discussion and recommendations for these patient categories for reasons explained above. We focus on evidence for benefit that came from studies that used patient-centered outcomes—we ignored studies that exclusively used physiologic endpoints. We also limit the discussion to the two main ventilator settings, V_T and PEEP.

16.2 Tidal Volume

For many years it was common practice to use a high V_T up to 15 ml/kg predicted body weight (PBW) during intraoperative ventilation in the OR. As such, anesthesiologists were able to keep lung tissue recruited for as much as possible—this facilitated gas exchange, and prevented the need for higher oxygen fractions (FiO_2) or PEEP.

This strategy was initially adopted in the ICU, where in its earliest years mechanical ventilation was mostly the domain of anesthesiologists. However, several animal experiments suggested harm from higher V_T. These preclinical findings induced a series of randomized clinical trials in patients with ARDS, showing that a simple reduction in the size of the V_T to as low as 6 ml/kg PBW confers into great improvements in outcome [1]. Consequently, anesthesiologists and intensivists reconsidered their ventilation approaches, and massively adopted the so-called low V_T ventilation, at least in patients with ARDS.

16.3 Tidal Volume in the Operating Room

16.3.1 Benefit of a Lower V_T

Numerous observational studies showed an association of the size of the V_T used during intraoperative ventilation with the occurrence of postoperative pulmonary

complications [2, 3]. Then three randomized clinical trials showed that a reduction in the size of V_T prevented development of postoperative pulmonary complications and improved outcomes [4–6]. While these three trials also used a higher PEEP alongside a lower V_T, the finding of an individual patient data metaanalysis suggests that it was the lower V_T that protected the patients from developing postoperative pulmonary complications, and not the higher PEEP [2].

16.3.2 Challenges of a Lower V_T

Intraoperative ventilation with a lower V_T can result in alveolar instability, increasing the risk of atelectasis and cyclic opening and closing of alveolar unit. Next, using a lower V_T mandates the use of a higher respiratory rate (RR). However, CO_2 production is often low in anesthetized patients, which allows using a lower V_T without having to increase the RR much—this is important as anesthesiologists tend to 'over–ventilate' their patients [7].

16.3.3 Temporal Changes in the Size of V_T

Observational studies have shown temporal changes in the size of the V_T used during surgery [7, 8]. Indeed, intraoperative V_T has decreased from as high as 12 ml/kg PBW to 8 ml/kg PBW in recent years. Nevertheless, low V_T (<8 ml/kg PBW) ventilation remains underused [7]. This may be due to poor individualization, as sometimes anesthesiologists still use a fixed V_T, most often 500 ml [7]. This often translates into a too high V_T, in particular in shorter individuals, most often the females [9]. Interestingly, anesthesiologist also tend to ventilate obese patients with too high V_T, probably because they remain titrating the V_T against the actual body weight instead of PBW [7].

16.3.4 Current Recommendations

Currently, a lower intraoperative V_T of between 6 and 8 ml/kg PBW is recommended [10]. Though it can be argued that an 'intermediate' V_T of up to 10 ml/kg PBW is protective, and leastwise is not harmful [11]. In patients undergoing thoracic surgery, a lower V_T is advised with one-lung ventilation (see also Chap. 25).

16.4 Tidal Volume the Intensive Care Unit

16.4.1 Benefit of a Lower V_T

Observational studies in critically ill patients without ARDS found reductions in the size of V_T to be associated with a lower risk of pulmonary complications, a shorter duration of ventilation, and a shorter ICU and hospital length of stay [12–14]. One

recent study, however, failed to show benefit from ventilation with a lower V_T (4–6 ml/kg PBW) when compared to ventilation with an intermediate V_T (8–10 ml/kg PBW) [15]. Of note, in that study patients were often on a spontaneous mode of ventilation early after the start of mechanical ventilation. As the size of V_T is much less controllable with spontaneous ventilation than with controlled ventilation, it is not surprising that the V_T size in the two groups was fairly comparable soon after they were allowed to breath spontaneously. What can also be acknowledged is that the size of V_T in the intermediate V_T arm of the study was not so high, and much lower than in the observational studies that triggered this randomized clinical trial.

16.4.2 Challenges of a Lower V_T

Ventilation with a lower V_T may increase the risk of atelectases. It may also increase sedation needs and hence the risk of delirium [16], and could be associated with more patient-ventilator asynchrony [17]. In addition, compensatory inspiratory efforts could cause self-inflicted lung injury [18]. Last but not least, the use of a higher RR, needed with the use of a lower V_T, may be associated with worse outcomes [19]. It should be noted, though, that this all was not found in the recent study mentioned above [15].

16.4.3 Temporal Changes in the Size of V_T

Over the years, in critically ill patients the size of V_T has decreased progressively. Indeed, V_T size has declined from >12 ml/kg PBW [20] to <8 ml/kg PBW [21, 22]. Nevertheless, also in these patients, low V_T ventilation remains largely underused [21, 22]. It could be that also in this setting, at times, the V_T is erroneously titrated against the actual body weight. And also, in the ICU there are remarkable and persistent differences in the size of V_T between the sexes, both in patients with- [23] and without ARDS [24]. This may be due to the fact that patients' height, necessary to calculate the PBW, can be difficult to measure and often the shorter individuals are at risk of overestimation [25].

16.4.4 Current Recommendations

Currently, there are no strict recommendations for V_T in critically ill patients without ARDS. A higher V_T, i.e., >10 ml/kg PBW is probably not acceptable [26]. Based on the current evidence, we recommend to use a lower V_T (6–8 ml/kg PBW), certainly in patients who are receiving controlled ventilation. We also

emphasize to titrate V_T against the PBW, and not the actual body weight, and to implement proper estimation of patients' height for accurate calculation of the PBW.

16.5 Positive End-Expiratory Pressure

Partial lung collapse, or atelectasis, negatively affects gas exchange. It may also result in repeated opening and closing of adjacent lung tissue, which could cause or increase lung injury. Numerous preclinical studies have shown that PEEP can recruit these unstable lung units, but at the same time also lead to overdistension of other lung regions. For a long time it was very unusual to use PEEP in the operating room. This may be due to the association of PEEP with hemodynamic instability requiring fluidic expansion and mandating initiation of vasopressors.

In patients with ARDS, PEEP can clearly improve oxygenation, thereby reducing the need for a high FiO_2. Three randomized clinical trials tested the hypothesis that ventilation targeting an "open lung" with higher PEEP (median ~15 cm H_2O) improves outcomes in patients with ARDS [27–29]. These three studies, however, failed to show benefit from higher PEEP. One metaanalysis using the individual patient data of these three studies, however, suggested mortality benefit of ventilation with higher PEEP in patients with moderate or severe ARDS [30], while a signal for harm was observed in patients with mild ARDS. A more recent randomized clinical trial in patients with moderate or severe ARDS showed harm from a strategy that used higher PEEP plus aggressive recruitment maneuvers [31].

Meanwhile, there was a clear tendency to using some PEEP, at times higher PEEP, in patients with healthy lungs, both in the OR and in the ICU.

16.6 PEEP in the Operating Room

16.6.1 Benefit of Higher PEEP

Several randomized clinical trials in various surgical populations suggested benefit from intraoperative ventilation with higher PEEP with respect to occurrence of postoperative complications [4–6] We need to acknowledge, however, that in these three studies it was not only PEEP that was different between the two study arms, as in the higher PEEP strategy V_T was low, and in the lower PEEP strategy V_T was high. It could be argued that the putative benefit of higher PEEP was blurred by simultaneous use of a lower V_T. Therefore, two randomized clinical trials compared intraoperative ventilation with lower PEEP (<5 cm H_2O) with higher PEEP (12 cm H_2O, or more) at a lower V_T [32, 33]. These two studies failed to show a reduction in postoperative outcomes in non-obese patients [32] and obese patients [33].

16.6.2 Challenges of Higher PEEP

Use of a higher PEEP may compromise the cardiac function and cause hypotension. This is exactly what was found in the two studies mentioned above, in which intraoperative ventilation with lower PEEP was compared with higher at a lower V_T: in non-obese patients the proportion of patients that received intraoperative vasopressors increased from 51 to 62% [32], and in obese patients this proportion increased from 45 to 50% [33]. While in theory a higher PEEP strategy could increase the risk of barotrauma, this was not found in these two studies.

16.6.3 Temporal Changes in PEEP

PEEP is increasingly used in the OR. One study evaluating intraoperative ventilator management in more than 80,000 patients from 96 studies over a time span of 30 years showed a slight increase in PEEP [34]. This might depend form the positive findings with higher PEEP in animal studies, and the results of the abovementioned studies that compared intraoperative ventilation with higher PEEP/lower V_T with ventilation with lower PEEP/higher V_T. Additionally this might depend from the lower values of PEEP allowed by specific ventilators manufacturers which range between 2 and 5 cm H_2O.

16.6.4 Current Recommendations

The debate about the best level of PEEP during surgery has not yet settled. New studies were initiated to determine if PEEP titrated to the best respiratory system compliance, or driving pressure, would be better than a standard low PEEP [35, 36]. Meanwhile, we suggest to use the lowest PEEP possible, and only use higher PEEP as a rescue, i.e., in case of hypoxemia refractory to increase in FiO_2. Probably, 5 cm H_2O PEEP is sufficient, and acceptable to use. It is uncertain whether higher levels of PEEP should be used in patients undergoing closed abdominal surgery or robotic surgery, conditions during which there can be an impressive cephalad shift of the diaphragm [37]. Several studies are currently planned, and here we would like to advise to use higher PEEP as suggested above: only use higher PEEP as a rescue, i.e., in case of hypoxemia refractory to increases in FiO_2.

16.7 PEEP in the Intensive Care Unit

16.7.1 Benefit of Higher PEEP

Since the beginning of intensive care, optimizing oxygenation and CO_2 removal were seen as the targets of mechanical ventilation. Notably, there were periods in which targets for oxygenation were higher than normal levels. Use of PEEP, and higher PEEP, fitted well in these approaches as the use of a higher pressure at the

end of expiration can greatly improve aeration of the lung, and prevent partial lung collapse. Use of PEEP, and specifically higher levels of PEEP, was also stimulated by the idea that an 'open lung' strategy could prevent lung injury, as shown in several preclinical studies using models that mimicked the scenario of a critical illness.

One metaanalysis of studies in critically ill patients without ARDS showed no benefit for PEEP when compared to lower PEEP or no PEEP [38]. It should be noted that the studies included in the analysis were small, of poor quality, and most of these were earlier than the use of a clear definition for ARDS. One recently published randomized clinical trial in patients at risk for ARDS compared a ventilation with higher PEEP (8 cm H_2O) with ventilation with a lower PEEP (between 0 and 5 cm H_2O) [39]. In this non-inferiority study, ventilation with lower PEEP was not inferior, compared to ventilation with higher PEEP, with respect to the duration of ventilation. This study did show a better oxygenation with the higher PEEP strategy, and also an increase, albeit not statistically significant, in the use of rescue therapies for hypoxemia. Also after adding this study, the findings of the metaanalysis were confirmed [40].

16.7.2 Challenges of Higher PEEP

Partial lung collapse in patients without ARDS is much less extensive than in patients with ARDS. At least in theory, it could be that relatively higher PEEP is needed to recruit a similar amount of lung tissue in patients with healthy lungs as compared to patients with ARDS. Since lung tissue in patients with healthy lungs is more compliant, this translates in a greater lung volume and intra thoracic pressure change, for the same PEEP, than for patients with ARDS. Therefore, the hemodynamic effects of higher PEEP could be more present in critically ill patients with healthy lungs [41]. Last but not least, it is possible that the use of higher PEEP could delay extubation, since it is common practice to extubate at a low PEEP [42].

16.7.3 Temporal Changes in PEEP

Alike in surgery patients in the OR, higher PEEP is increasingly used in critically ill patients in the ICU, including in patients not having ARDS [34]. This was also shown in several successive worldwide service reviews that focused on ventilator management [43–45]. By now, more than half of critically ill patients with healthy lungs receive ventilation with PEEP >5 cm H_2O, but there are regional differences [46].

16.7.4 Current Recommendations

Recommendations regarding PEEP in patients with healthy lungs are lacking. Our recommendation is to avoid the routine use of higher PEEP in these patients. Ventilation with lower PEEP (<5 cm H_2O) may be as sufficient as ventilation with a higher PEEP.

16.8 Conclusions

We summarized the current evidence for the use of lower V_T and higher PEEP in surgery patients in the OR, and in critically ill patients with healthy lungs in the ICU. Use of a lower V_T is appealing, because it is imaginary that a larger volume can cause harm through overdistension of lung tissue, with a great potential to harm the delicate pulmonary structures. This outweighs one major disadvantage of ventilation with a lower V_T, a worsening oxygenation. The use of a higher PEEP is also appealing, because it is imaginary that a higher PEEP recruits a larger part of the lung, and prevents repeated opening and closing of alveolar units. However, benefit of higher PEEP is lacking in patients with healthy lungs, and the side effects of ventilation with higher PEEP, hemodynamic instability, may force us to be less in the favor of using this strategy. Future studies in specific patient groups may show benefit of ventilation with higher PEEP.

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PEEP Setting in ARDS

17

Emanuele Rezoagli and Giacomo Bellani

17.1 Introduction

Positive end-expiratory pressure (PEEP) is the positive pressure applied during expiration in controlled or assisted mechanical ventilation: it ensures a pressure in the alveoli higher than the atmospheric one, at the end of expiration, with the primary aim of preventing alveolar collapse.

In this chapter, we refer to the "extrinsic PEEP," i.e. the PEEP level set on the ventilator. This should not be confused with intrinsic or auto-PEEP, which is the alveolar pressure at the end of an incomplete exhalation due to airflow obstruction or flow limitation.

PEEP is considered a keystone ventilatory treatment for the management of ARDS in critically ill patients. Ashbaugh and colleagues reported the first formal description of the beneficial effect of PEEP in reversing hypoxemia in Acute Respiratory Ristress Syndrome (ARDS) in 1967 [1].

Overall, PEEP increases the intrathoracic pressure, which is variably distributed to the lung and to the chest wall according to their respective compliance.

In this chapter we will describe at first the pathophysiological effects of PEEP application in ARDS. Subsequently, we will describe how PEEP may be selected according to different targets and the main clinical results obtained with different methods.

E. Rezoagli · G. Bellani (✉)
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy
e-mail: emanuele.rezoagli@unimib.it; giacomo.bellani1@unimib.it

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17.2 Pathophysiology: Beneficial Effects of PEEP

In ARDS, PEEP allows to prevent part of the alveolar collapse by counteracting elevated surface tension caused by surfactant impairment, superimposed pressure due to increased lung weight and the chest wall recoil.

These effects avoid alveolar overdeflation during expiration and then reduce intrapulmonary shunt. Technically, the role of PEEP is the prevention of the alveolar derecruitment [2], while recruitment is an "inspiratory phenomenon." At the same time, since an increase in PEEP is typically associated to an increased inspiratory pressure, the two phenomena (recruitment and avoidance of derecruitment) are often coupled. Alternatively, Recruitment Maneuvers (RM) may be applied in combination with PEEP titration under the rationale that the pressure required to open an alveolus is higher than the pressure which avoids derecruitment (hysteresis).

When PEEP is applied, the participation of some alveoli to the gas exchange is restored and the end-expiratory lung volume (EELV) increases. This usually leads to the decrease of the lung strain and to an improvement of the respiratory system compliance. In turn, the driving pressure is then reduced for the same tidal volume: this is desirable because of the robust association between a lower DP and a higher survival rate [3].

Furthermore, PEEP can minimize ventilator induced lung injury (VILI) by reducing atelectrauma (i.e. the cyclic alveolar opening and closing during tidal ventilation) and reducing lung heterogeneity and stress, leading to a more homogeneous ventilation with less stress raisers, that are neighbor regions to the lung units with different elastic interfaces.

17.3 Pathophysiology: Harmful Effects of PEEP

If PEEP is set inappropriately, it can exert harmful effects on both the respiratory and the cardiovascular systems.

High levels of PEEP can increase the right atrial pressure significantly. This can determine a decrease of the pressure gradient to venous return. Consequently, this leads to a reduction of the right preload—as first—and consequently of the left preload with the final decrease of cardiac output.

As any other pressure, PEEP tends to affect the lung regions with a higher compliance. Typically, in ARDS, while consolidated areas difficultly reopen regardless high PEEP settings, the non-dependent areas—open and well ventilated—are prone to overdistend, which can promote alveolar inflammation and injury. Moreover, depending on the balance between recruitment and ovedistension, PEEP may increase pulmonary vascular resistance, and hence increases the right afterload with risk of cor pulmonale. Finally, if alveolar pressure higher exceeds the capillary pressure, this may increase alveolar dead space because of the occlusion of capillaries, causing an impaired clearance of carbon dioxide.

17.4 Recommendations of PEEP Setting in ARDS

The current guidelines do not suggest a specific level or threshold of PEEP in ARDS. However, higher rather than lower levels of PEEP are suggested in moderate or severe ARDS with a conditional level of recommendation, coming from an individual patient data meta-analysis by Briel et al. [4]. In this study, the average levels of PEEP on day 1 were 15.3 (±3.4) and 9.0 (±3.1) cmH_2O in the higher and lower PEEP groups, respectively [5]. Despite these recommendations, PEEP levels routinely set in ARDS are concerningly low. In the LUNG SAFE median levels of PEEP were 8.3 and 10.1 cmH_2O in moderate and severe ARDS [6]. Analogously, in the recently published SAGE study, the authors confirm that lower average levels of PEEP are set in a selected population of ARDS patients with a $PaO_2/FiO_2 \leq 150$ mmHg in the USA [7].

Unfortunately, recommendation about the method on how to set PEEP are lacking and whether a technique is superior to another one is unknown. This is still a largely debated topic, on which we will focus in the remaining part of the chapter.

17.5 Strategies Aimed at Titrating PEEP at Bedside

17.5.1 NIH PEEP/FiO_2 Combination Tables

One approach to titrate PEEP according to the severity of ARDS was proposed for the trial on tidal volume by the National Institutes of Health ARDS Network. Increasing PEEP in discrete steps (up to 18–24 cmH_2O) was associated with increasing FiO_2 (also in discrete steps) within a range of 0.3–1.0 targeting normoxemia.

Subsequently, the same investigators proposed a higher PEEP/FiO_2 table—in contrast to the first one labeled as "lower". In order to test the possible positive protective role of PEEP against the contributors of VILI (i.e. volutrauma, atelectrauma, barotrauma, and biotrauma), the two tables were compared in two randomized controlled trials [8, 9]. Patients treated with higher levels of PEEP showed an improved arterial oxygenation compared to the lower PEEP groups, suggesting higher lung recruitment with higher levels of PEEP, but no difference in mortality was observed.

One of the assumptions underpinning the use of a PEEP/FiO_2 table is the relationship between improved oxygenation and lung recruitment, which is rather weak. On one hand, if the increase of PEEP leads to an increase of EELV, some of the pulmonary perfusion is directed to areas that now regain ventilation. This determines a decrease in the right to left shunt, allowing for a better arterial oxygenation. On the other side, PEEP may decrease oxygenation because of the increase in PVR and overdistension. This may potentially diverge the blood flow to the collapsed lung units and then increase the right to left shunt. Indeed, not all patients show an

increase in oxygenation after an increase in PEEP. However, the use of a PEEP/FiO_2 tables, mandates an increase in PEEP along with FiO_2, neglecting the individual patient response (both in oxygenation and respiratory mechanics) [10]. At the same time, tables reduce the risk of an improper increase in FiO_2 uncoupled from PEEP.

This is supported by the evidence that an improved oxygenation—as a consequence of increased PEEP—is associated with an improved survival rate, as shown in a secondary analysis of two large clinical trials [11].

When evaluating gas exchange, $PaCO_2$ and dead space should not be forgotten, given their sensitivity to ventilation perfusion mismatch. Suter et al. suggested, in 1975, that the decrease in the dead space fraction was associated with an increase of the oxygen transport and with an increase of the static compliance [12]. Indeed, an increase of $PaCO_2$ with PEEP, at constant minute ventilation, indicating increased dead space, might be caused by reduced alveolar perfusion and overdistention.

17.5.2 Respiratory Mechanics: Compliance and Driving Pressure of the Respiratory System (Cpl,rs)

Compliance of the respiratory system has been proposed as a target for PEEP titration since 1975 when, in two separate studies Suter and Falke reported that the increase of PEEP was associated with increases of FRC, Cpl,rs, and oxygenation [12, 13]. However, the use of Cpl,rs as a target to optimize PEEP setting is based on the assumption that the increase in Cpl,rs reflects increased lung volume due to alveolar recruitment, while overdistension leads to a loss in compliance. This mainly depends on the amount of the lung recruitable volume and on the opening pressures of the poorly inflated and not inflated lung areas. Moreover, this assumes that the chest wall and abdominal mechanics are unaffected by PEEP application. Furthermore, another potential misleading factor is the intra-tidal alveolar opening and closing that may overestimate the contribution of PEEP on the increased Cpl,rs.

More recently, it was proposed a PEEP optimization based on the driving pressure (DP), which equals the ratio between the tidal volume and the Cpl,rs. Cpl,rs is proportional to EELV and hence to the “baby lung” size. In summary, DP is a proxy of the tidal volume delivered over the aerated lung, and it is independently associated with mortality [3]. Furthermore, in a recent reanalysis of the ALVEOLI and ExPress trial, Yehya and coworkers compared the association between mortality and the changes in PaO_2/FiO_2 and DP following protocolized ventilator changes. The investigators observed a more robust association with mortality according to changes in DP compared to changes in oxygenation, suggesting the primary associative role of DP with mortality [14].

The concept of looking for a lower DP (or higher compliance) as a target to set PEEP, appeared recently challenged by the results of the ART trial [15]. This reported that a RM followed by a decremental PEEP trial [16], targeting the Cpl,rs, increased mortality. We believe that this study does not rule out either using higher PEEPs or targeting lower DPs. In the ART trial other factors might have contributed to the higher mortality, such as the use of an aggressive RM of 60 cmH_2O (later

decreased 50 cmH_2O) lasting several minutes overall, requiring neuromuscular blocking agents, important fluid expansion and an additional RM employed after PEEP titration. Moreover, PEEP was set at 2 cmH_2O above the vaule associated with lowest DP (or best Cpl,rs), which may have led to overdistension of the non-dependent lung regions [10, 15].

17.5.3 Pressure–Volume (PV) Curve and Lung Volume Measurements

Some authors proposed the use of the lower inflection point of the pressure–volume curve as a threshold above which PEEP should be set. This should minimize the atelectrauma [17]. The main limitations of this strategy are the need for deep sedation and (likely) neuromuscular blocking, the uncertainly in identification of inflection point in some patients and the fact that the opening pressures are located on the entire inspiratory limb of the PV curve. As the alveolar closing pressure are lower that the opening pressure [18], the PV loop shows a relevant hysteresis and provide a rationale for the application of a recruitment maneuver before increasing PEEP [10]. Other investigators proposed the use of the expiratory limb to titrate PEEP. This seems more physiologically sound as compared to the use of the inspiratory limb. However, the lungs of ARDS start to collapse at high pressure levels following a gravitational gradient (i.e. from the dependent to the non-dependent lung regions).

Change in lung volume during PEEP titration (see also Chap. 35) may also allow to assess the gain in aerated volume following a PEEP change. Dilutional gas techniques (including helium or nitrogen washin/washout) have been used to measure EELV. When PEEP is increased, EELV will necessarily increase (even without any recruitment), proportionally with compliance. If the increase of EELV exceeds the value predicted (as the product of compliance by PEEP change), the extra volume is considered to reflect the aeration of new lung units [19]. Recently, Chen and proposed a method based on an abrupt PEEP decrease from 15 to 5 cmH_2O. If the increased exhaled volume was higher than the expected (based in compliance), the difference among these volumes would correspond to the "PEEP recruited volume." The ratio between the compliance of the recruited volume and the compliance at low PEEP was termed "recruitment to inflation ratio," a tool that may characterize lung recruitability at bedside [20].

17.5.4 Stress Index (SI)

The SI is a mathematical description of the slope of the pressure–time curve during volume controlled ventilation (with square inspiratory flow), described by the formula $Paw = a * t^b + c$. The SI is the exponent b. This is calculated on some ventilators or must be "visually evaluated" in the other cases. Values of SI lower than one indicate that compliance progressively increases during insufflation (intra-tidal

recruitment), while values higher than one indicate overdistension. Hence, the optimal value for SI is considered to be 1 [21]. Grasso et al. showed a higher Cpl,rs with lower levels of inflammatory biomarkers when the stress index was used as a target of PEEP titration as compared to the lower PEEP/FiO_2 table [22].

17.5.5 Transpulmonary Pressure

The concept behind the use of transpulmonary pressure to titrate PEEP derives from the concept that, while part of the pressure expands the lungs, it expands also the chest wall, in a variable proportion. During conditions of PV curve shift to the right (i.e. obesity) or in the presence of a low chest wall compliance (i.e. abdominal distension, pleural effusion or burns) an increased amount of the airway pressure is spent to distend the chest wall—therefore the pressure distending the alveoli will be decreased. For this reason, esophageal (as a surrogate of pleural) pressure has been used to dissect the contribution of the chest wall and the lung on the global airway pressure. Two main methods are used to estimate the transpulmonary pressure: one is based on the absolute pressure values, while others rely on the swings caused by tidal insufflation [23].

In the EPVent trial, Talmor and colleagues demonstrated that PEEP adjusted a ording to esophageal pressure—aimed to achieve an end-expiratory transpulmonary pressure level between 0 and 10 cmH_2O, depending on FiO_2—improved oxygenation and Cpl,rs, and caused a non significant reduction in 28-day mortality as compared to the lower PEEP/FiO_2 table (17% vs 39%, $p = 0.055$) [24]. Given that the absolute values of PEEP in the intervention group were significantly higher, in the subsequent EPVent-2 trial, the authors compared the esophageal pressure-guided PEEP adjustment with the higher PEEP/FiO_2 combination table. No difference between the groups was observed for any outcome endpoint [25]. Interestingly, in an ancillary analysis, the effect of treatment on 60-day mortality was affected by baseline severity of multiorgan dysfunction, with a lower mortality in the esophageal pressure-guided group in the presence of lower APACHE-II score [26].

17.5.6 Lung Imaging

Specific chapters of this book are dedicated to the imaging techniques summarized below. CT scan has been a major advancement in the study of the regional distribution of lung gas in patients with ARDS. Different groups took advantage of CT scan to better understand the relationship between lung mechanics, mechanical ventilation and distribution of lung aeration and collapse [27, 28]. Given the need of patient transferral and radiological exposure, lung CT analysis can be used, for PEEP

setting, for selected cases and for research purposes as it is hardly suitable for the daily clinical routine.

Constantin and coworkers differentiated ARDS based on radiological imaging techniques, in focal versus diffuse ARDS and set higher PEEP in patients with a diffuse disease. This did not lead to a reduction of mortality in the global population, but this result was blurred by the high mortality rate in patients that were misclassified [29].

Lung ultrasound has been recently proposed for PEEP titration as it is a reliable technique to evaluate lung recruitment—however, its use does not provide reliable information on overdistension [30].

Recently, the electrical impedance tomography (EIT, see also Chap. 33) has been suggested because of its potential to discriminate regional lung derecruitment and overdistension. EIT is radiation free and can be performed at bedside. Furthermore, EIT can provide a dynamic information on the regional distribution of the tidal ventilation and can infer on the change in the EELV following PEEP change [31]. While one approach is based on the regional changes of compliance during a decremental PEEP trial [32, 33], we proposed an approach based on an incremental PEEP trial where a "diagnostic" RM was used before each PEEP increase (Fig. 17.1). This aims at obtaining a stable EELI signal during the tidal ventilation [34].

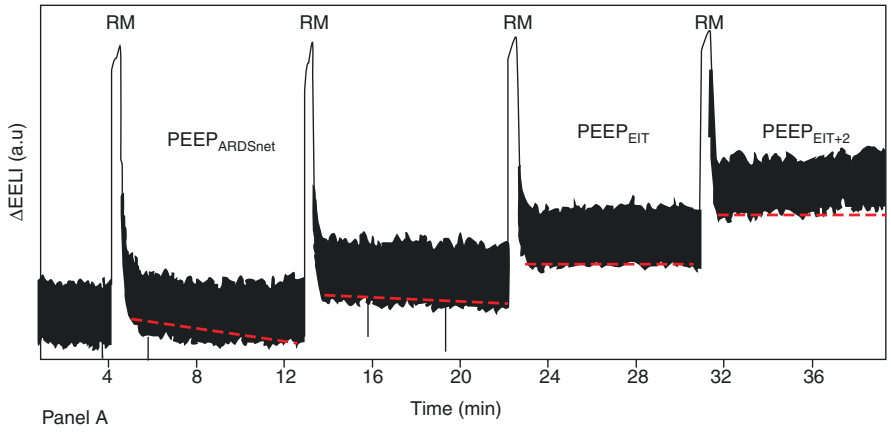

Fig. 17.1 This image shows the behavior of lung volumes during positive end-expiratory pressure (PEEP) changes interspersed by "diagnostic" recruitment maneuvers (RM), monitored by EIT. The first RM, after which the PEEP level is left unchanged, shows the presence for alveolar recruitment, given the increase in end-expiratory lung volume. However, the PEEP level is not sufficient to prevent the alveolar derecruitment, as the EELV returns to the baseline value. Increasing PEEP by 2 + 2 cmH_2O allows to maintain alveolar stability after recruitment. (Reproduced under Creative Common Licence from [34])

Novel data indicates the possibility to image the distribution of pulmonary perfusion and this might allow a PEEP optimization that takes into account the ventilation perfusion mismatch [35].

17.5.7 PEEP: The Role of ARDS Phenotypes

In the recent years, a deeper understanding in the biology of ARDS and in the radiological presentation allowed to characterize different phenotypes within the same syndrome.

Calfee et al. reported that two different phenotypes of ARDS exist, based on clinical and laboratory data. The authors observed that only the hyperinflammatory one showed a decreased mortality rate by using higher levels of PEEP [36]. These findings were recently confirmed in a reanalysis of both randomized clinical trials on ARDS and in the LUNG SAFE real-life data set [37].

17.6 Conclusion

PEEP is a key parameter during mechanical ventilation in ARDS. PEEP increases aerated lung volume and may avoid derecruitment. However, PEEP can lead to alveolar overdistension and hemodynamic instability. Current guidelines suggest higher levels of PEEP in patients with moderate–severe ARDS. Different strategies to titrate PEEP include NIH PEEP/FiO_2 combination tables, incremental or decremental PEEP protocols, esophageal catheter or advanced techniques of lung imaging such as EIT.

Main targets of PEEP titration include oxygenation, respiratory mechanics, and more recently the imaging of the balance between lung recruitment versus derecruitment.

The advancement of the biological and radiological understanding of the ARDS is helping toward a more tailored characterization of ARDS definition and management, suggesting which ARDS phenotypes can benefit the most from higher versus lower PEEP levels.

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Mechanical Ventilation in Brain Injured Patients

18

Lorenzo Peluso, Elisa Bogossian, and Chiara Robba

18.1 Introduction

Patients with brain injury frequently need mechanical ventilation (MV), both to protect the airways and to maintain adequate oxygenation and carbon dioxide (CO_2) levels to minimize secondary brain damage. Moreover, neuro-patients often develop respiratory complications, such as acute respiratory distress syndrome (ARDS) which occurs in up to 20–38% of cases [1]. The pathophysiologic relationship behind brain and lung interaction is complex [2]; moreover, due to the heterogeneity of brain injury and the lack of evidence, there are no ideal ventilatory strategies or precise gas exchange targets that can unanimously be considered beneficial.

In this chapter we will describe and explore possible approaches to manage mechanical ventilation in acute neurological patients focusing on their advantages and side effects.

18.2 Indications for Invasive Mechanical Ventilation in Brain Injured Patients

The decision to intubate patients with brain injury should be primarily focused on the protection of airways to prevent aspiration, the level of consciousness, and level of intracranial pressure (ICP). Particularly, patients with loss of the airway

L. Peluso · E. Bogossian
Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

C. Robba (✉)
Department of Surgical Science and Diagnostic Integrated, Policlinico San Martino Genova, IRCCS for Oncology and Neuroscience, Genoa, Italy

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protective reflexes, Glasgow Coma Scale (GCS) ≤ 8, and a substantial increase in ICP or signs of brain herniation should be considered for intubation. Moreover, in the presence of concomitant extra-neurologic conditions who require intubation, this maneuver should not be delayed.

Literature is scarce regarding the use, indications, and timing of non-invasive ventilation (NIV) in brain injured patients. NIV can potentially reduce the need for invasive ventilation, but it can also increase intrathoracic pressure, without protecting airways and control CO_2 levels; in the recent consensus statement providing recommendations on mechanical ventilation in patients with acute brain injury, the panel noted that the quality of evidence was very low and did not reach consensus on the use of non-invasive respiratory support in this population [3]. However, the use of high-flow nasal cannula oxygen therapy may be considered in patients with hypoxemic respiratory failure that is refractory to conventional supplemental oxygen [3].

18.3 Ventilatory Strategies and Targets

18.3.1 Ventilator Settings

Regarding the ventilator setting, there is a lack of studies that assessed whether one modality of ventilation is better than others, and mostly in traumatic brain injury (TBI), which show that patients ventilated in pressure-regulated volume control mode present less fluctuation in ICP and $PaCO_2$ [4]. The use of positive end-expiratory pressure (PEEP) is a cornerstone in the management of respiratory failure and protective ventilation strategies to prevent atelectasis and optimize oxygenation. Its use has been challenged in brain injured patients [5], as it can increase intrathoracic pressure and reduce cerebral venous outflow; however, PEEP seems to be safe as long as it does not cause hyperinflation and hemodynamic stability is maintained [3]. As consequence, the European Society of Intensive Care Medicine (ESICM) consensus recommends that patients with brain injury without ARDS both without ICP elevation and with ICP elevation "PEEP-insensitive" should be ventilated with a PEEP level equal to patients without brain injury [3]. In patients with brain injury, with or without ARDS and without a raise in ICP, a lung protective mechanical ventilation strategy with low tidal volume and plateau pressure is strongly recommended to minimize respiratory complications, whereas the question still remains regarding its use in patients with brain injury and unstable ICP (Fig. 18.1); in this latter situation, ventilatory settings should be considered case by case and additional neuromonitoring is warranted to assess cerebral metabolism.

18.3.2 Oxygenation and Carbon Dioxide Targets

The blood levels of oxygen (PaO_2) and CO_2 should be strictly monitored, as both play pivotal roles in brain homeostasis. Peripheral oxygen saturation should be kept >94% [6], both hypoxemia and hyperoxemia should be avoided and PaO_2 should be maintained between 80 and 120 mmHg regardless of ICP levels [3].

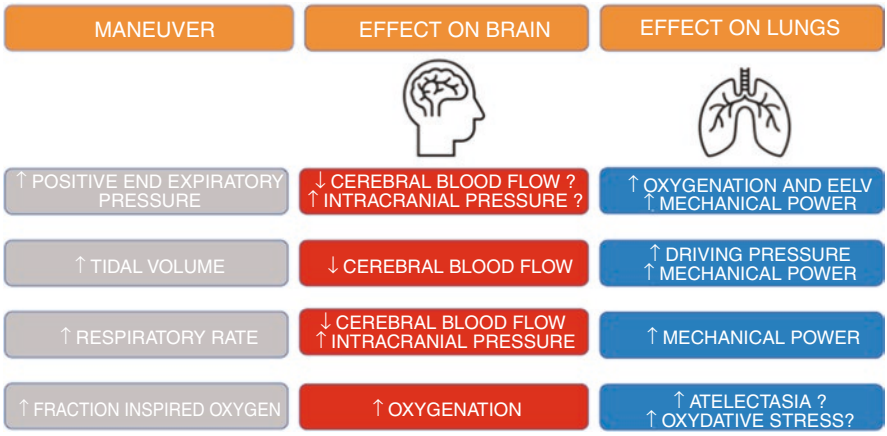

Fig. 18.1 Effects of ventilatory parameters on brain and lungs. *EELV* end-expiratory lung volume

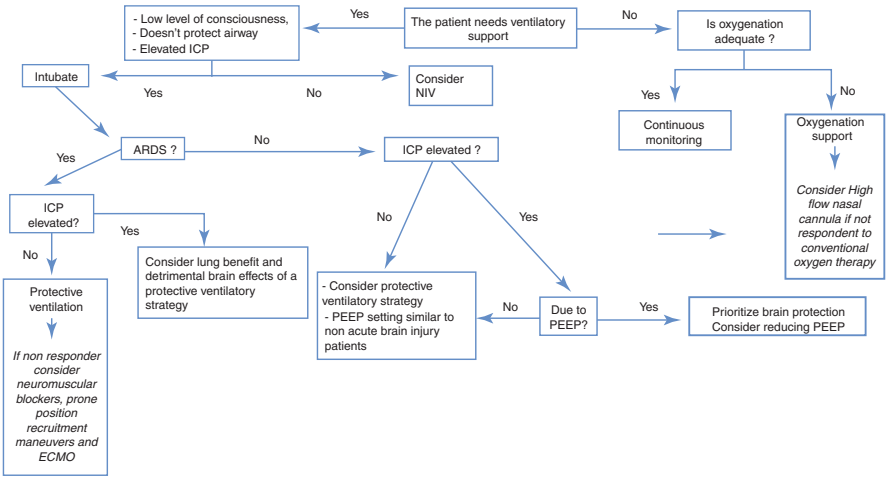

Fig. 18.2 Possible algorithm of ventilatory management in brain injured patients. *ICP* intracranial pressure, *NIV* non-invasive ventilation, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *PEEP* positive end-expiratory pressure

CO_2 should be strictly and frequently assessed in brain injured patients, as it can strongly modify the cerebral perfusion being a major determinant of cerebral blood flow (CBF) [7]. As stated in the ESICM recommendation, the optimal target in brain injured patients without ICP elevation is 35–45 mmHg. Short-term hyperventilation should be used only when refractory ICP elevation and signs of brain herniation are present [3]. In such cases, a target of $PaCO_2$ = 30 mmHg is warranted, and the possible effects on brain perfusion should be strictly monitored [8].

Figure 18.2 shows a decisional tree proposed by the authors for the management of ventilatory support in acute brain injury patients.

18.4 Rescue Interventions for Refractory Respiratory Failure

There are several strategies that can be used to optimize ventilation and oxygenation in patients with respiratory failure refractory to conventional treatment, such as recruitment maneuvers, prone positioning, the use of neuromuscular blockers and extracorporeal membrane oxygenation (ECMO). However, these strategies may not be appropriate for patients with acute brain injury due to their possible impact in ICP, cerebral perfusion pressure, and CBF.

Recruitment maneuvers can improve oxygenation, alveolar recruitment and reduce ventilation/perfusion mismatch. On the other hand, these maneuvers may increase ICP in patients with impaired autoregulation by compromising cerebral venous return [9]. A study enrolling patients with subarachnoid hemorrhage (SAH) or TBI concomitant to ARDS found that pressure controlled recruitment maneuvers improved PaO_2/FiO_2 ratio without significant detrimental effects on ICP and CPP [9]. However, due to the paucity of data, no recommendations were provided regarding recruitment maneuvers in acute brain injury by the recent ESICM guidelines [3], and these should be reserved only to specific cases of refractory severe hypoxemia secondary to de-recruitment.

In ARDS patients, prone position has been shown to improve oxygenation and to reduce mortality. In acute brain injury patients, the use of prone position may be challenging due to the risk of malpositioning of neuromonitoring, drains and to the risk of increased intrathoracic pressure and ICP [10]. In small studies with SAH and TBI patients prone positioning improved oxygenation with variable degrees of increase in ICP [10, 11]. Therefore, in specific cases, prone positioning may be considered under strict monitoring of ICP [3].

ECMO can be an interesting strategy in ARDS patients that failed to respond to conventional approaches. However, anticoagulation is needed to avoid circuit clotting and bleeding is still an important complication of this procedure. For this reason, ECMO is usually contra-indicated in patients with intracranial hemorrhage. However, some case reports suggest that ECMO may be used in patients with head injury as a rescue therapy for ARDS [12, 13], reducing or avoiding the initial bolus of heparin, and in cases with low risk of intracranial bleeding.

18.5 Weaning and Tracheostomy

The burden of delayed extubation and extubation failure is high in acute brain injury patients, leading to prolonged time of mechanical ventilation and ICU length of stay, and high mortality rates [14].

The decision to extubate and/or wean a patient from ventilatory support after acute brain injury should be guided by several neurological and non-neurological factors such as the expected clinical trajectory of the patients, the expected complications of the underlying acute brain injury process, the level of consciousness, and the ability of the patient to protect airway (adequate cough, gag, and swallowing reflexes) [3]. Patients should also have a stable hemodynamic and metabolic status, have adequate oxygenation and pulmonary function [15]. A spontaneous breathing

test is usually recommended for the ICU population who stayed mechanically ventilated for >24 h [15].

Patients who have persistently reduced the level of consciousness and those who fail one or more extubation attempts should be tracheostomized to facilitate weaning and respiratory care. The appropriate timing to perform a tracheostomy is still unknown, but in acute brain injury patients, early tracheostomy may reduce ICU and hospital length of stay [16].

18.6 Ventilation in Neuromuscular Disease

Most neuromuscular diseases cause progressive respiratory muscle weakness and respiratory failure. Acute respiratory failure is a common life-threatening complication of acute onset neuromuscular diseases, and may exacerbate chronic hypoventilation in patients with neuromuscular disease. Standard management includes oxygen supplementation, physiotherapy, cough assistance, and, whenever needed, antibiotics and intermittent positive pressure ventilation.

Long term non-invasive mechanical ventilation is a fundamental step for ventilator management as it improves gas exchange, quality of life, and survival.

Different interfaces are available, nasal, buccal or full-face devices, with a variety of styles and sizes, and portable ventilators with good leak compensation and with a variety of modes allow the management of these patients out of the hospital.

However, muscles weakness causes reduction in vital capacity, which, together with rib cage distortion with inspiratory effort, may lead to failure of non-invasive devices and need for invasive ventilation.

Randomized trials aimed to elaborate evidence-based practice for the use of non-invasive versus invasive mechanical ventilation are warranted and are not available at present.

These trials should anticipate variations in treatment responses according to disease condition, in particular acute onset versus acute exacerbation on chronic neuromuscular diseases according to the presence or absence of bulbar dysfunction.

Weaning failure is frequent because of muscle weakness. Applying conventional weaning strategies in neuromuscular diseases is generally difficult. Weaning process can be conducted in protocols including “T” piece or Pressure Support Ventilaton.

In patients that require invasive mechanical ventilation or who cannot protect airway and are not able to be weaned from the ventilator, tracheostomy should be performed.

18.7 Conclusions

There is still a lack in scientific evidence in the management of mechanical ventilation in brain injured patients. Nevertheless, some recommendations based on pathophysiologic assumption, comorbidities, and the clinical setting should guide the

clinicians through an individualized approach to provide the best way to manage such patients.

Further high-quality studies are necessary to better define ventilatory strategies and gas exchange targets that may impact the outcome.

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Invasive and Non-invasive Ventilation in Patient with Cardiac Failure

19

Aurora Magliocca and Giuseppe Ristagno

19.1 Introduction

Acute cardiac failure consists in a rapid deterioration of the cardiac function, potentially life-threatening, often associated with lung congestion and acute respiratory failure (ARF). Severe hypoxemia is frequently observed in patients with acute cardiogenic pulmonary edema and cardiogenic shock, two conditions requiring prompt support of respiratory function. The application of positive airways pressure is the cornerstone of respiratory assistance in patients with ARF due to cardiac failure, supported by pathophysiology and clinical evidence.

19.2 Pathophysiology of Respiratory Failure During Acute Cardiac Failure

19.2.1 Acute Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema is characterized by a rapid increase in pulmonary capillary hydrostatic pressure, with consequent disturbance of the Starling equilibrium. Indeed, the hemodynamic profile of cardiogenic pulmonary edema is often characterized by high filling pressure (i.e. pulmonary capillary wedge pressure), high blood pressure, and normal/low cardiac output. As a result, fluid accumulation can be observed in (1) perivascular and peribronchial interstitial tissues, known as *interstitial edema* until (2) fluid moves across the epithelium into the alveoli producing *alveolar edema*.

A. Magliocca · G. Ristagno (✉)
Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
e-mail: aurora.magliocca@unimi.it; giuseppe.ristagno@unimi.it

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Edema fluid in the alveolar units alters surfactant function and increases surface tension. The likelihood of alveolar collapse at low lung volumes increases, preventing ventilation of the fluid-filled alveolar units. Until perfusion of these units is preserved, an increase in pulmonary shunt and ventilation to perfusion mismatch leads to hypoxemia.

In this context, pathophysiology of ARF due to cardiogenic pulmonary edema foresees multiple mechanisms:

1. The pressure–volume curve of the lungs with pulmonary edema is shifted to the right and downward leading to a significant reduction of functional residual capacity (FRC) and increased lung stiffness (i.e. reduced compliance) [1].
2. Edema formation in the peribronchial region causes an increase in airway resistance. A greater change in airway resistance has been demonstrated in experimental models of cardiogenic pulmonary edema compared to noncardiogenic ones [2].
3. These pathophysiological alterations result in increased work of breathing (WOB) and increased oxygen demand from the respiratory muscles, potentially creating an imbalance between oxygen delivery and consumption [3]. Indeed, in patients with cardiorespiratory disease the oxygen cost of breathing has been reported to increase markedly, being as high as 25% of total oxygen consumption compared to normal values of 1–3% [4].

19.2.2 Cardiogenic Shock

If acute cardiac failure progresses further, towards a decrease in cardiac output, this determines tissue hypoperfusion together with pulmonary edema. The hemodynamic profile of cardiogenic shock is characterized by low cardiac output, low blood pressure, and high filling pressure (i.e. central venous pressure and pulmonary capillary wedge pressure). The inadequate peripheral tissue oxygen delivery results in reduced mixed venous oxygen saturation (SvO_2) and increased lactate levels.

Cardiogenic shock is usually associated with ARF. In addition to the pathophysiology of respiratory failure described in the previous section, other mechanisms should be mentioned. The reduction in lung perfusion causes an increase in ventilation-perfusion mismatch (dead space increases). Moreover, the decreased mixed venous saturation leads to a worse hypoxemia for the same pulmonary shunt fraction.

19.3 Rationale for Positive Airway Pressure in Patients with Cardiac Failure

The application of positive end-expiratory pressure (PEEP) increases intrathoracic pressure (ITP) impacting both respiratory and hemodynamic function, as represented in Fig. 19.1.

Higher ITP increases FRC recruiting collapsed alveolar units and improving lung compliance. Oxygenation is improved by a decrease in pulmonary shunt and

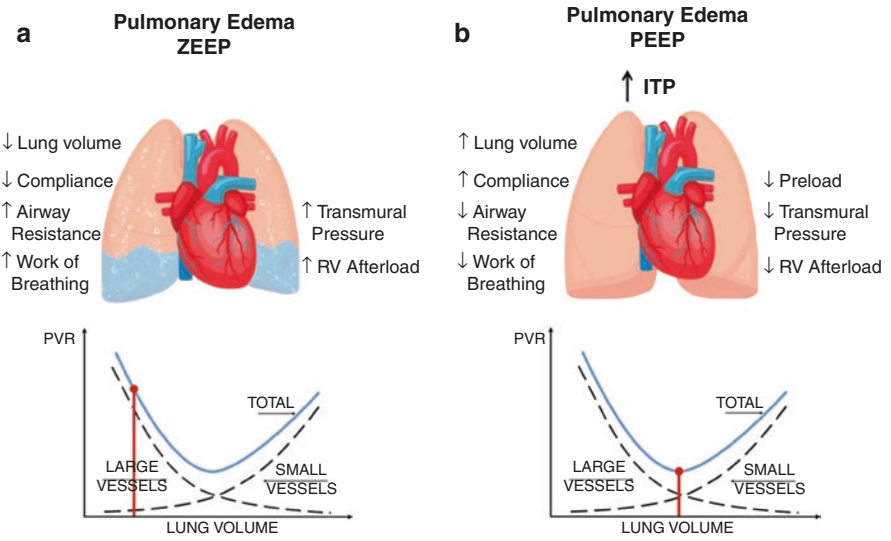

Fig. 19.1 Pathophysiology of respiratory failure during cardiogenic pulmonary edema (**a**) and physiologic effect of positive airways pressure on respiratory mechanics and hemodynamics (**b**). *ZEEP* zero end-expiratory pressure, *PEEP* positive end-expiratory pressure, *ITP* intrathoracic pressure, *RV* right ventricle, *PVR* pulmonary vascular resistance

ventilation to perfusion mismatch. An increase in ITP also results in a significant decrease in airway resistance and WOB [5]. Thanks to these mechanisms and reduced respiratory drive, the application of continuous positive airways pressure (CPAP) with different levels of PEEP: 5 and 10 cmH_2O, despite not providing any "active" inspiratory support reduces inspiratory negative ITP swings generated by the respiratory muscles, with a positive effect on left ventricular afterload [5].

The main hemodynamic effect of increasing ITP is a decrease of the systemic venous return to the right ventricle (RV) and a reduction of pressure gradient for systemic outflow from the left ventricle (LV), as outlined below.

19.3.1 Right Ventricle

Positive airways pressure may affect RV preload and afterload. The pressure gradient for the RV venous return is represented by the difference between the mean systemic filling pressure (upstream pressure), and the right atrial pressure (RAP), which is the downstream pressure [6]. Positive airway pressure increases both ITP and RAP, decreasing venous blood flow, RV filling and cardiac output (Fig. 19.2a) [9]. Although, typically, the effect of ITP on preload is attributed to an increase in RAP causing a reduction of the pressure gradient for venous return, the actual mechanism is probably far more complex since ITP increases in parallel both RAP and MSFP. In a condition of normal cardiac function, an adaptive response to PEEP has been demonstrated to reduce vascular capacitance leading to an increase in MSFP with no impact on the pressure gradient (MSFP − RAP) [9], and during

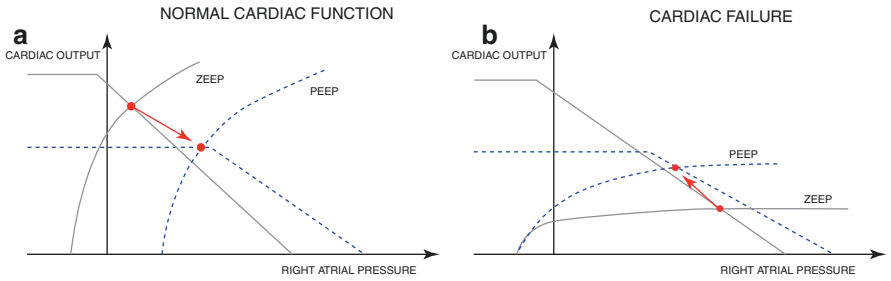

Fig. 19.2 Effect of positive airway pressure application on cardiac output in case of normal cardiac function and cardiac failure, according to Guyton's model [6, 7] where cardiac output (curved lines) or venous return (straight lines) are plotted as a function of Right Arterial Pressure. Since cardiac output and venous return must equate, the only possible "working" status is the intersection of the two lines. With a normal heart function (**a**), PEEP (dashed lines) moves downwards and to the right the curve of venous return, so that for a given right arterial pressure (clinically reflected by central venous pressure, CVP) the venous return will be lower. Also the cardiac output curve is shifted to the right since right atrial pressure here is represented as measured relative to atmosphere (intramural pressure), while transmural pressure is lower. When right atrial pressure is measured relative to the extramural pressure (transmural pressure) cardiac function curve is not modified by PEEP levels of up to 15 cm H_2O [8]. The new working point (red point) in (**a**) becomes located on the plateau of the new venous return curve, showing not only that cardiac output decreases, but also that any increase in cardiac function will not further increase cardiac output. In the presence of cardiac failure (**b**) the effect of PEEP on venous return is similar. However, since PEEP decreases afterload, ventricular function is improved, cardiac output function is steeper and the two curves cross at a higher value of cardiac output (or venous return). *ZEEP* zero end-expiratory pressure, *PEEP* positive end-expiratory pressure

cardiogenic pulmonary edema an aggressive management of systemic blood pressure would also influence MSFP.

Experimental data also suggest that deformation of vasculature may account for the increased venous resistance responsible for the detrimental effect of ITP on venous return [10]. Finally, the reduction in RV size [11], decreasing the wall tension, decreases cardiac oxygen consumption.

The effect of ITP on RV afterload reflects its effect on lung volumes. Indeed, the U-shaped relationship between lung volume and pulmonary vascular resistance (PVR) suggest that PEEP can recruit collapsed alveolar units, leading to an increase in lung volume and reduction of PVR (Fig. 19.1b). At higher lung volumes (i.e. alveolar overdistention) compression of the small vessels increases PVR thus increasing RV afterload.

19.3.2 Left Ventricle

A higher ITP may reduce LV afterload by lowering transmural pressure (P_{TM}) [12]: this is the pressure gradient across the wall of the LV, the difference between the extramural and the intramural pressures. The LV P_{TM} is defined as systolic arterial pressure (SAP) minus ITP (LV P_{TM} = SAP − ITP).

In patients with cardiac failure, the application of CPAP may reduce LV P_{TM} and afterload by decreasing the negative ITP swings generated by respiratory muscles thereby improving LV function (Fig. 19.2b) [5, 13]. Increasing ITP may increase cardiac output [5, 13–15] and left ventricular ejection fraction [16] in patients with congestive heart failure. Interestingly, the increase in cardiac output is mainly due to an increase in stroke volume, whereas heart rate falls significantly during CPAP [5, 13–16].

However, there is considerable variation in patients' response to PEEP application, even within the same study: an increase, decrease, or no change in cardiac output were observed in different patients [13–15]. The positive effect of PEEP on cardiac output is most likely to occur when LV systolic function is altered and the filling pressure is higher (i.e. pulmonary capillary wedge pressure ≥ 12 mmHg) [15]. This suggest that the positive hemodynamic effect of raising ITP is not only due to a lower LV P_{TM}, but LV preload reduction may also contribute by shifting the LV in a more favorable position on its compliance curve. Finally, the heterogeneous transmission of PEEP to the intrathoracic structures could further contribute to the variability observed [17].

19.4 Non-invasive Positive Pressure Ventilation for Cardiogenic Pulmonary Edema: Clinical Evidence

Several randomized controlled trials (RCTs) support the clinical application of positive airways pressure for patients with cardiac failure to improve outcomes [18–20]. It appears equivalent whether positive pressure is delivered as CPAP or with a pressure support as NIV, since no RCT has demonstrated a clear advantage of one technique over the other [19]. CPAP or NIV consistently produce a greater physiologic improvement, compared to standard oxygen therapy, as shown by the reduction in respiratory rate observed after 1 h of treatment in all studies of this systematic review [19].

Interestingly, likely because of improved respiratory mechanics, CPAP alone (which per-se does not increase alveolar ventilation) is able to decrease $PaCO_2$ and improve pH [20]. Although cardiac output was not assessed in any of these RCTs, positive airways pressure application improved global hemodynamic, since arterial blood pressure did not change while heart rate significantly decreased within the first hour of treatment [18–20].

The largest multicenter RCT on the application of NIV in patients with acidotic (pH < 7.35) cardiogenic pulmonary edema (3CPO trial) shows that ventilatory support delivered for 2 h by either CPAP (5–15 cmH_2O) or NIV (inspiratory pressure: 8–20 cmH_2O; expiratory pressure: 4–10 cmH_2O) provides an early improvement of dyspnea while reducing hypercapnia, acidosis and heart rate compared to standard oxygen therapy, after 1 h of treatment [18]. The positive physiologic effect of NIV was not associated with reduction of intubation rate and 7 and 30 days mortality. Several factors including the high crossover rate (~15% of patients randomized to standard oxygen therapy crossed over to NIV) and the low severity of the patient

population (Baseline mean PaO_2 in the three groups ≈100 mmHg) might explain the lack of efficacy of NIV on mortality observed in this trial.

Still, the latest systematic review subsequently published incorporating 3CPO trial and other 23 RCTs (2664 patients) show that NIV application reduces endotracheal intubation rate and hospital mortality, with an uncertain duration on hospital length of stay [19]. The incidence of acute myocardial infarction was not different in patients randomized to NIV (CPAP or bilevel ventilation) compared to standard medical therapy. In addition, no difference has been observed in systolic, diastolic, and mean blood pressure between the two groups after 1 h of therapy, while respiratory distress was improved by reducing respiratory rate and increasing oxygenation after 1 h of treatment [19]. In the subgroup of patients with hypercapnic cardiogenic pulmonary edema the optimal ventilation technique and the effects on outcomes should be further explored.

The ERS/ATS clinical practice guidelines on the use of NIV in ARF due to cardiogenic pulmonary edema recommend either bilevel ventilation or CPAP for these patients [21]. The 2019 Cochrane Systematic Review shows that positive airways pressure reduces hospital mortality (RR 0.65; 95% CI 0.51–0.82) and endotracheal intubation rates (RR 0.49; 95% CI: 0.38–0.62) compared to standard medical therapy alone for cardiogenic pulmonary edema.

Finally, the beneficial effect of positive airway pressure application in patients with ARF due to cardiogenic pulmonary edema has been demonstrated also in the pre-hospital setting [20–22]. Out-of-hospital use of CPAP is feasible, improves hypoxemia and reduces the endotracheal intubation rate [20–22].

19.5 Non-invasive and Invasive Positive Pressure Ventilation for Cardiogenic Shock

The evidence supporting the use of NIV in patients with cardiogenic shock is limited; indeed the official 2017 ERS/ATS guidelines do not provide recommendations on the use of NIV in these patients [21].

A recent prospective registry reported that invasive mechanical ventilation is used in 49.5% of patients admitted in cardiac ICU for cardiogenic shock, increasing up to 60.3% when this is due to AMI, and 65.9% in case of mixed shock [23].

Given the lack of specific evidence in cardiogenic shock, it seems reasonable to tailor respiratory support according to clinical presentation. Indeed, clinical features of cardiogenic shock, such as altered mental status, hemodynamic instability and hypoperfusion often compromise the ability to sustain spontaneous breathing, making NIV a less suitable option compared to invasive ventilation.

19.6 Ventilation in the Post Cardiac Arrest Period

After return of spontaneous circulation (ROSC), following cardiac arrest (CA), patients are prone to develop a post-reperfusion state characterized by systemic inflammation and multiple organ dysfunction known as post-CA syndrome. Among

the clinical features of this syndrome, hypoxic-ischemic brain injury represents the main cause of death and long-term disability. Furthermore, a high incidence of lung injury/lung edema in the post-CA period has been shown [24, 25]: almost 50% of CA survivors develop ARDS within 48 h after hospital admission [24], reflecting the relevance of lung-brain interaction.

An adequate setting of mechanical ventilation, with the primary aim of maintaining oxygen and CO_2 tensions within physiologic range, is essential to reduce the secondary brain injury.

Post-resuscitation care starts immediately after ROSC. However, in the prehospital setting the optimal ventilation strategy and specific oxygenation target remain uncertain.

In hospital, the current ERC-ESICM guidelines [26] recommend a lung protective ventilation strategy using a tidal volume (V_T) of 6–8 mL kg^{-1} of ideal body weight. This is based on a propensity-adjusted analysis of data from 256 out-of-hospital CA patients, showing that a lower V_T during the first 48 h after ROSC was independently associated with a favorable neurological outcome (OR, 1.61; 95% CI, 1.13–2.28) and more ventilator- and shock-free days. Interestingly, 38% of patients received an average $V_T > 8$ ml/kg of predicted body weight (PBW) over the first 48 h, while just 4% received an average $V_T \leq 6$ ml/kg PBW during this time [27].

The recommendation on oxygenation target in the post-ROSC phase is to titrate inspired oxygen concentration to maintain an SpO_2 of 94–98% or PaO_2 of 75–100 mmHg [26]. Although experimental studies suggest that hyperoxemia is associated with worse neurological outcome after CA, clinical studies have shown conflicting results [28, 29]. In the COMACARE trial [29] there was no difference between normoxemia (PaO_2 75–113 mmHg) or moderate hyperoxemia (PaO_2 150–188 mmHg) in neuronal injury as assessed by the blood levels of neuron specific enolase at 48 h after ROSC.

Finally, regulation of CO_2 tension in the arterial blood ($PaCO_2$) is crucial since it represents a major determinant of cerebral blood flow and brain O_2 delivery. Indeed, hypocapnia and hypercapnia cause cerebral vasoconstriction or vasodilation respectively, which impact cerebral blood flow and intracranial pressure (see also Chap. 18). The ERC-ESICM recommendation is to maintain a $PaCO_2$ between 35 and 45 mmHg [26]. Although there is conflicting evidence on the association between CO_2 levels and brain injury [29, 30], the neuroprotective effect of mild hypercapnia is currently under investigation in the TAME trial, a phase III multicenter RCT (NCT03114033).

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COPD and Severe Asthma

20

Lise Piquilloud and Damian Ratano

20.1 Pathophysiology

Obstructive respiratory diseases include chronic obstructive pulmonary disease (COPD) and asthma. In emphysematous COPD patients, decrease in elastic lung recoil due to parenchyma destruction can lead to small airways collapse during expiration and increased resistance to expiratory airflow [1]. Intermittent acute exacerbations, characterized by acute worsening of respiratory symptoms, are part of the clinical course of obstructive respiratory diseases and may require, in the most severe cases, invasive mechanical ventilation. Acute exacerbation of COPD (AE-COPD) is characterized by an increase in secretions, inflammation, and some degree of bronchospasm. Acute asthma (or asthma attack, AA) is mainly characterized by severe bronchospasm leading to very high airways resistance, some degree of inflammation and presence of mucus in the airways [2]. Although the pathophysiology of exacerbation differs in AE-COPD and AA, these pathologies share two major characteristics: increased airways resistance and airflow limitation. Therefore, the management of ventilatory support during AE-COPD and AA is quite similar.

Airflow limitation causes air to be trapped in the alveoli at the end of expiration. End-expiratory lung volume is higher than functional residual capacity and alveolar pressure is higher than atmospheric pressure (or than the set positive end-expiratory

L. Piquilloud (✉)
Adult Intensive Care Unit, University Hospital of Lausanne, Lausanne, Switzerland

Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
e-mail: lise.piquilloud@chuv.ch

D. Ratano
Adult Intensive Care Unit, University Hospital of Lausanne, Lausanne, Switzerland
e-mail: damian.ratano@chuv.ch

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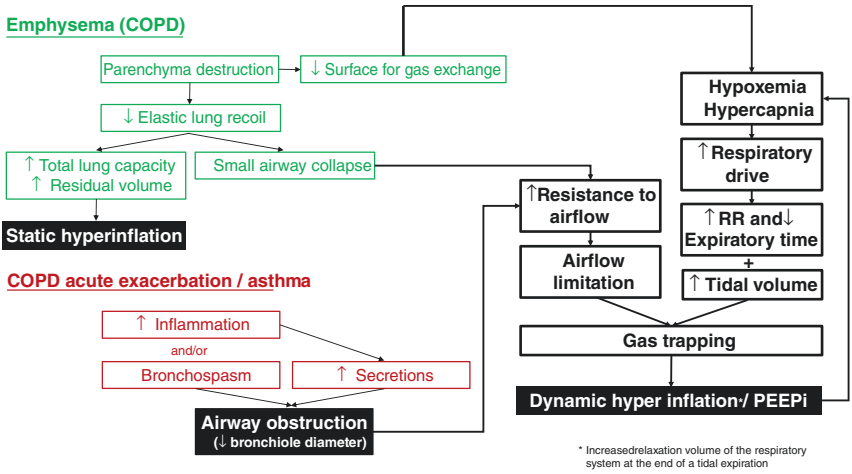

Fig. 20.1 Physiopathology of respiratory failure in COPD exacerbation and asthma attack. *PEEPi* intrinsic PEEP

pressure, PEEP). This phenomenon is called dynamic hyperinflation or dynamic airtrapping and the amount of pressure above atmospheric pressure (or set PEEP) at the end of expiration is called intrinsic positive end-expiratory pressure (PEEPi) or auto-PEEP [3]. In clinical practice, dynamic hyperinflation is exacerbated by increased respiratory drive, tidal volumes, and respiratory rate (and thus short expiratory time) typical of respiratory distress. The pathophysiology of AE-COPD and AA is schematized in Fig. 20.1.

Patients with AE-COPD and AA are at risk of dynamic hyperinflation both during spontaneous breathing and controlled ventilation. Dynamic hyperinflation has major adverse effects. The risk of barotrauma is increased (because of increased intraalveolar pressure) and hemodynamics can be altered (because of increased intrathoracic pressure and consecutive decrease in venous return) [4]. When overdistension occurs, hypercapnia and hypoxemia result from altered ventilation over perfusion matching and respiratory system compliance decreases. Diaphragm contractile function is also reduced because of diaphragm flattening. In addition, during assisted breathing, dynamic hyperinflation increases work of breathing (WOB) and causes poor patient-ventilator synchrony (delayed triggering, ineffective efforts, and late expiratory cycling). Figure 20.2 summarizes the main adverse effects of dynamic hyperinflation, in general and during assisted breathing (in gray).

20.2 Respiratory Support Strategies in General

Invasive mechanical ventilation is associated with high mortality in AE-COPD exacerbation and AA [5]. Non-invasive ventilation (NIV) as the first line respiratory support has been associated with decrease in intubation rate and

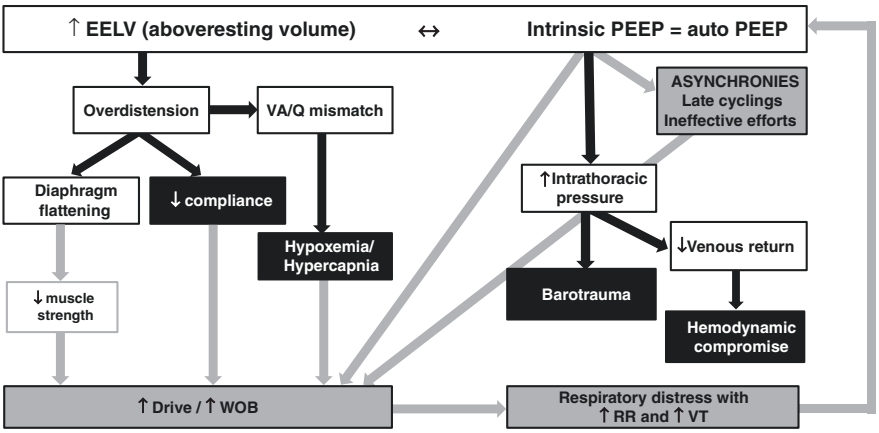

Fig. 20.2 Adverse consequences of dynamic hyperinflation. *EELV* end-expiratory lung volume, *VA/Q* ventilation over perfusion ratio, *WOB* work of breathing, *RR* respiratory distress, V_T tidal volume. Gray color for assisted breathing

mortality in AE-COPD [6, 7] compared to standard oxygen therapy. NIV is thus recommended as the first line ventilatory support in AE-COPD in the absence of absolute contraindication or indication for immediate intubation [8]. To note, AE-COPD patients intubated because of NIV failure have no increased mortality compared to those intubated without previous NIV trial [9, 10]. The first line treatment for AA is the administration of high-dose inhaled bronchodilators (β2 mimetics). Even if sometimes used by experienced teams in AA [11], the role of NIV in AA is still debated and not recommended in the most recent guidelines [8]. In severe AA, severe hypotension can follow intubation (because of lung hyperinflation and hypovolemia) and mortality in intubated asthmatic patients remains high. Therefore, in AA, intubation should be limited to patients with immediate life-threatening conditions (respiratory arrest, bradypnea, patients exhausted and/or with severe and worsening hypercapnia or major respiratory distress despite adequate medical treatment or altered level of consciousness).

The increased use of NIV in AE-COPD and aggressive treatment of AA with inhaled bronchodilatators has significantly reduced intubation rate [12] in the last decades. In the most severe cases, intubation is, however, still needed to allow sufficient gas exchanges and/or because of respiratory exhaustion, mainly for AE-COPD. As dynamic hyperinflation has major adverse effects, the goal when ventilating an intubated obstructive patient is to limit as much as possible the amount of air trapped in the lungs at the end of the breathing cycle. The aim is not to normalize gas exchanges and, in particular, not to normalize hypercapnia [13], as this would enhance dynamic hyperinflation. As a corollary, permissive hypercapnia has been associated with improved outcome in severely obstructive patients with status asthmaticus [13].

20.3 Controlled Invasive Ventilation of the Obstructive Patient: Goals, Monitoring of Dynamic Airtrapping and Settings Strategies

In the acute phase of exacerbation, controlled ventilation is required in intubated obstructive patients. To limit dynamic hyperinflation, permissive hypercapnia (and respiratory acidosis) has often to be tolerated. pH between 7.25 and 7.30 can clearly be considered as safe [13] and much lower values have been demonstrated to be well tolerated [13, 14] for prolonged periods of time.

Dynamic hyperinflation can be quantified by performing an end-expiratory occlusion, during which the inspiratory and expiratory valves of the ventilator are closed. As a consequence, in the absence of total airway closure and at the equilibrium, the pressure measured in the ventilator circuit equals airway and alveolar pressures. The end-expiratory pressure measured during occlusion is called total PEEP ($PEEP_{tot}$). When dynamic airtrapping is present, $PEEP_{tot}$ is higher than set PEEP. In other words, PEEPi or auto-PEEP is present. PEEP tot and PEEPi are correlated with the volume of air higher than functional residual capacity trapped in the lungs at the end of expiration. Limiting dynamic hyperinflation, hence, means maintaining PEEPtot and PEEPi as low as possible. Without performing an end-expiratory occlusion, dynamic airtrapping can be suspected (albeit not quantified) by looking at the flow-time curve on the ventilator screen. When the flow-time curve does not come back to zero at the end of expiration, dynamic airtrapping is very likely. Another parameter important to monitor when ventilating obstructive patients is plateau pressure (Pplat), measured by an end-inspiratory occlusion (see Chap. 4). Pplat equals alveoli pressure at the end of inspiration. It depends from respiratory system compliance, the amount of assist delivered by the ventilator and $PEEP_{tot}$. The aim during controlled ventilation is maintaining Pplat lower than 28 or maximum 30 cmH_2O or even lower.

As for intubated patients [15] in general, using a pressure or a volume regulated mode to ventilate obstructive patients was not demonstrated as having an impact on outcome. Volume assist control has, however, advantages in this situation. First, tidal volume and minute ventilation are not influenced by variations in the degree of obstruction and thus by variations in bronchospasm severity. Second, if a constant inspiratory flow is used, volume assist control allows relatively easy monitoring of respiratory system mechanics including airway resistance. Independently from the type of ventilatory mode used (pressure or volume regulated), minute ventilation has to be minimized and sufficient time must be available for expiration to limit dynamic hyperinflation [16]. This can be obtained by delivering relatively low tidal volumes (6–8 ml/kg of predicted body weight) and low respiratory rate, as for example 12 breaths/min [17, 18]. The aim is delivering minute ventilation of maximum 10 l/min or even less when obstruction is particularly severe. This strategy is called controlled hypoventilation. It leads to permissive hypercapnia [14]. It is important to note that decreasing respiratory rate to values lower than 12 breaths/min, even if contributing to limit dynamic hyperinflation, only has a minor additional effect [19, 20] when delivered minute ventilation is low. Using respiratory

rates lower than 12 breaths/min should be considered only in the most severe cases when Pplat remains higher than 30 cmH_2O with already low minute ventilation and/or when dynamic hyperinflation related complications (as for example barotrauma) have already occurred. Expiratory time is also a key value when ventilating an obstructive patient. In order to provide enough time for expiration, it is important, in addition to set a low respiratory rate, to target a low inspiration to expiration ratio (*I*:*E*) as, for example, 1:4 instead of the physiological value of 1:2. It must be underlined here that, for a given and stable minute ventilation, increasing expiratory time only has a relatively limited effect on dynamic hyperinflation [16]. Reducing respiratory rate is much more efficient. Suppressing the inspiratory pause is another option to increase the time available for expiration. This, however, suppresses the quasi-static measurement of Pplat, which is a very valuable continuous monitoring tool even though, in the presence of increased resistance, it often overestimates static Pplat. Suppressing the inspiratory pause during volume assist control ventilation should only be considered in the most severe obstructions. Table 20.1 (upper part) summarizes the general principles to set the ventilator when ventilating an obstructive patient in the acute phase of the disease with a controlled mode. If, with tidal volume between 6 and 8 ml/kg of predicted body weight and respiratory rate of 12 breaths/min, plateau pressure is lower than 28 cmH_2O and $PEEP_{tot}$ is low enough, a slow and step by step increase in respiratory rate can be considered to improve blood gases. For each incremental step, Pplat and $PEEP_{tot}$ must be monitored. If these increase, respiratory rate should be decreased again.

Table 20.1 General principles to set the ventilator when ventilating an obstructive patient with a controlled mode and with pressure support

Objective: Reducing hyperinflation, not normalizing gas exchanges = controlled hypoventilation/permissive hypercapnia				
	Aim ↓ Minute ventilation to ↓ volume to exhale	Aim ↑ Expiratory time ↓ Inspiratory time	Aim ↓ Work of breathing	Monitoring and targets
Controlled ventilation	• Limit V_T (6–8 ml/kg PBW) • Low respiratory rate	• ↑ Inspiratory flow (VAC) • ↓ *I*:*E* ratio (1:4 to less) • No inspiratory pause? (VAC)		• Minute ventilation <10 l/min • Low PEEPi • Plateau pressure < 28–30 cmH_2O
Assisted ventilation	• Limit pressure support level/ no overassist • Target low V_T (max 8 ml/kg PBW)	• Expiratory trigger threshold >25–30% (earlier opening of expiratory valve)	• Adequate level of PEEPe to avoid/limit ineffective efforts	• Low V_T and minute ventilation • Patient-ventilator synchrony

V_T tidal volume, *PBW* predicted body weight, *VAC* volume assist control, *PEEPe* extrinsic positive end-expiratory pressure, *PEEPi* Intrinsic positive end-expiratory pressure

Few data is available regarding the setting of extrinsic PEEP (PEEPe) in obstructive patients during controlled ventilation and this remains a controversial topic. Fundamentally, the use of PEEPe in obstructive patients during controlled ventilation reduces expiratory driving pressure and thus expiratory flow. It can thus act as a significant obstacle to expiration and enhance dynamic airtrapping. However, this essentially occurs when PEEPe is higher than or close to PEEPi. As long as PEEPe remains lower than 80% of PEEPi, at least in the presence of expiratory flow limitation, no increase in dynamic hyperinflation is due to the use of PEEPe [21]. In addition, some amount of PEEPe helps preventing atelectasis during invasive ventilation and improves oxygenation. Three different patients phenotypes can be described when we consider the use of moderate levels of PEEPe in obstructive invasively ventilated patients [22]. First, patients in whom using a moderate level of PEEP is well tolerated and not associated with any increase in $PEEP_{tot}$ and Pplat until a PEEPe threshold is reached. Second, patients in whom any increase in PEEPe is responsible for an increase in $PEEP_{tot}$ and Pplat. Finally, a third group of patients, in whom a moderate amount of PEEPe is associated with a paradoxical effect of decreased $PEEP_{tot}$ and Pplat also exists. Although the last phenotype represents a minority of the obstructive patients, response to a moderate level of PEEPe in obstructive disease during controlled ventilation cannot be predicted a priori and each patient should have a cautious trial of PEEPe. A practical approach to set PEEPe in obstructive patients during controlled ventilation is to start with PEEPe at 0 cmH_2O and to progressively increase PEEPe using a step by step strategy while monitoring $PEEP_{tot}$ and Pplat. As soon as $PEEP_{tot}$ and Pplat increase, PEEPe titration should stop and PEEPe should be reduced to the previous step. The rational behind the titration of PEEPe despite the risk mentioned above is to use PEEPe as tolerated in order to prevent atelectasis. This strategy is, however, mostly valid for COPD patients. In asthmatic patients, the risk of worsening dynamic hyperinflation even with a small amount of PEEPe is higher and, therefore, maximal caution should be exerted in this situation. Nonetheless, a low level of PEEPe (<5 cmH_2O) can be considered under very strict monitoring of PEEPtot and Pplat even in asthmatic patients [19].

20.4 Assisted Invasive Ventilation of the Obstructive Patient and Weaning Strategy

A prolonged duration of mechanical ventilation is associated with poor outcome [23]. Therefore, it is important to switch to assisted ventilation and to initiate the mechanical ventilation weaning process as early as possible. Pressure support ventilation is often used for the first step of de-escalation. At this phase, some level of obstruction is usually still present and particular attention should be paid to the tidal volumes with a goal of maximum 8 ml/kg of predicted body weight. Pressure support should be titrated accordingly and overassistance has to be avoided [24]. In the presence of residual airflow obstruction, it is important to pay particular attention to the expiratory trigger setting during pressure support. Because of airflow

obstruction the by default cycling off criterion of 25–30% of peak inspiratory flow is reached late. This decreases time available for expiration, leads to delayed (or late) cyclings, and favors dynamic hyperinflation. Increasing the cycling off criterion to 45–50% can help overcome this issue [25].

When PEEPi is present, the patient has to generate a significant inspiratory effort to overcome PEEPi before being able to trigger the ventilator [26]. In the presence of high PEEPi and/or when diaphragm weakness exists, ineffective efforts occur when inspiratory effort is not strong enough to both overcome PEEPi and trigger the ventilator [27]. The solution to reduce the effort intensity needed to trigger the ventilator is to set a PEEPe. This indeed counterbalances PEEPi, facilitates triggering, and improves patient-ventilator synchrony. PEEPe should, however, be kept lower than 80% of PEEPi. The difficulty is that PEEPi cannot easily be measured bedside during assisted ventilation. Practically, PEEPe should be titrated in a step by step approach with the aim of suppressing, or at least minimizing, ineffective efforts. Another clinical tool that can help setting PEEPe in obstructive patients during pressure support is to observe the use of accessory respiratory muscles, unbalanced PEEPi being related with more evident contraction of the accessory muscles due to stronger inspiratory efforts. Of note, during pressure support ventilation, the inspiratory trigger must also be set to the most possible sensitive value without generating autotriggering. Table 20.1 (lower part) summarizes the general principles to set the ventilator when ventilating an obstructive patient with pressure support.

As for all ventilated patients, readiness to wean should be screened every day [28] and a spontaneous breathing trial (SBT) should be performed when the readiness to wean criteria are present. In case of a successful SBT and in the absence of contraindication to extubation, the patient should be extubated as soon as possible [28]. In COPD patients, prophylactic NIV after extubation has been demonstrated as efficient in reducing reintubation rate [29].

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Ventilation in the Obese Patient

21

Pedro Leme Silva, Paolo Pelosi,
and Patricia Rieken Macedo Rocco

21.1 Introduction

Positive pressure mechanical ventilation (MV) is a life-support system essential for blood gas exchange. Positive pressure MV in obese patients deserves attention because, compared with lean patients, obese patients have lower functional residual capacity, alterations in the respiratory system due to changes in chest wall and lung mechanics, gas exchange impairment, as well as chronic local and systemic inflammation. MV parameters should be carefully adjusted and monitored overtime. The input ventilatory parameters can be adjusted by the health care provider, whereas outputs are those ventilatory parameters that depend not only on adjustments to the ventilator but also on lung conditions due to the effects of obesity. This chapter aimed to describe the input and output ventilatory parameters for obese patients (Fig. 21.1).

P. L. Silva · P. R. M. Rocco (✉)
Laboratory of Pulmonary Investigation, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
e-mail: pedroleme@biof.ufrj.br; prmrocco@biof.ufrj.br

P. Pelosi
Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy

Anesthesia and Critical Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy

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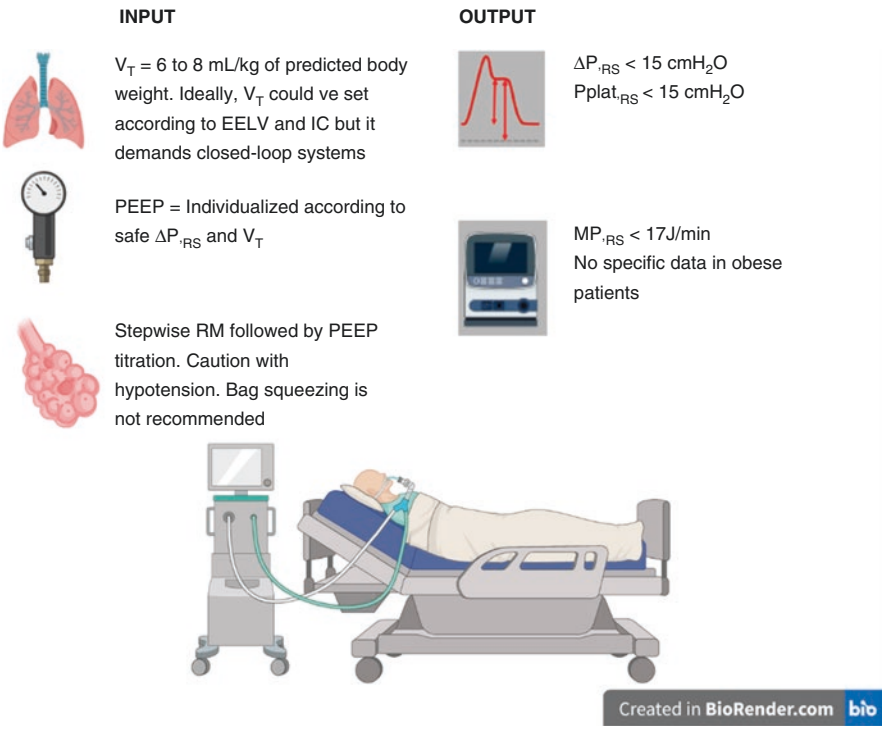

Fig. 21.1 Schematic representation of an obese patient under mechanical ventilation. The input ventilatory variables, those adjusted by the health care provider at the bedside, are (1) tidal volume (V_T) in protective range, from 6 to 8 mL according to predicted body weight; (2) individualized positive end-expiratory pressure (PEEP) setting according to safe ΔP and V_T; (3) stepwise recruitment maneuvers (RMs) followed by PEEP titration; and (4) bag squeezing is not recommended. The output ventilatory parameters, those ventilatory parameters that depend not only on ventilator adjustments but also on lung conditions due to the effects of obesity, are (1) $\Delta P_{,RS}$, which should be kept ≤15 cmH_2O; (2) plateau pressure should be kept ≤20 cmH_2O or whenever possible <27 cmH_2O; (3) mechanical power (MP) should be maintained <17 J/min. (Created with BioRender.com)

21.2 Input Ventilatory Parameters to Be Adjusted During Mechanical Ventilation in Obese Patients

21.2.1 Tidal Volume

Tidal volume (V_T) should be set according to the end-expiratory lung volume (EELV) or inspiratory capacity. Both are reduced in obesity conditions [1]. V_T adjustment to EELV can be more accurate at lower than higher positive end-expiratory pressure (PEEP), because higher PEEP increases EELV, including possible recruitment and/or overinflation. In a secondary analysis of a prospective multicenter study with 4968 patients [2], V_T normalized to predicted body weight

(PBW) was higher than expected, compared with actual body weight (11 mL/kg versus 5 mL/kg, respectively). Thus, as advocated for non-obese patients, the optimal V_T for obese patients with healthy lungs should be within the range of 6–8 mL/kg of PBW.

21.2.2 Positive End-Expiratory Pressure

The Protective Intraoperative Ventilation With Higher Versus Lower Levels of Positive End-Expiratory Pressure in Obese Patients (PROBESE) trial [3] showed that PEEP of 12 cmH_2O plus alveolar recruitment maneuvers (RMs) did not reduce postoperative pulmonary complications compared with PEEP of 4 cmH_2O. In a secondary analysis of the PROBESE trial, oxygenation improved, driving pressure decreased, and ventilation toward dependent lung areas redistributed in those patients whose PEEP was individualized by electric impedance tomography (EIT) (median [interquartile range], 18 [16–22 cmH_2O]) compared to fixed PEEP (4 cmH_2O). The clinical outcome was not evaluated. In a previous secondary analysis of the LAS VEGAS study, Ball et al. [4] showed that, overall, obese patients received relatively low PEEP levels (4 cmH_2O). Patients with class III obesity received higher PEEP levels (5 cmH_2O) and RMs by bag squeezing. On multivariate mixed logistic regression, bag squeezing was significantly associated with postoperative pulmonary complications.

Individualized PEEP setting by EIT has recently been proposed during intraoperative MV. Simon et al. [5] compared the effects of individualized PEEP set by EIT with PEEP 4 and PEEP 12 from the PROBESE trial on respiratory function and adverse events. Individualized PEEP set by EIT was associated with higher intraoperative oxygenation and lower driving pressure (i.e., better compliance of the respiratory system) but higher need for fluids and vasoactive drugs. These beneficial effects on respiratory function were lost after PEEP withdrawal, suggesting that individualized PEEP does not offer major advantages compared with fixed PEEP, but further research is needed to better clarify this important clinical issue [6].

21.2.3 Recruitment Maneuvers

In the literature, different forms of RMs have been applied in obese patients without acute lung diseases. Pirrone et al. [7] showed that an RM followed by PEEP titration improved lung volume, respiratory system elastance, and oxygenation in morbidly obese patients in medical and surgical intensive care units. RMs were performed in a stepwise fashion in which the baseline PEEP was 15 cmH_2O and, every 30 s, PEEP was increased by 5 cmH_2O up to 30 cmH_2O, together with 15 cmH_2O of pressure control. Nestler et al. [8] compared an RM followed by individualized PEEP (titrated using EIT) versus no RM and fixed PEEP of 5 cmH_2O. The RM consisted of peak airway pressure adjusted to 50 cmH_2O, PEEP of 30 cmH_2O, and a respiratory rate of 6 bpm for almost 90 s. The authors showed that, compared with fixed

PEEP of 5 cmH_2O, individualized PEEP resulted in improved oxygenation, respiratory system mechanics, ventilation distribution, and EELV during anesthesia. However, these beneficial effects disappeared during the early postoperative period. Thus, RMs followed by individualized PEEP did not prevent the reoccurrence of atelectasis after extubation, one of the features within the composite outcome of postoperative pulmonary complications.

21.3 Output Ventilatory Parameters to Be Monitored During Mechanical Ventilation in Obese Patients

21.3.1 Driving Pressure

Driving pressure is the difference between plateau airway pressure and PEEP during MV. It can also be defined as the normalization of V_T by respiratory system compliance (and hence, indirectly the reflects the ratio of V_T to lung size). To date, there are no data from large trials regarding safe driving pressure levels for obese patients undergoing MV. In this scenario, some theoretical comparisons may be worthwhile, taking into account normal ranges of chest wall and lung compliance in non-obese versus obese patients. With average chest wall and lung compliances of 200 and 100 mL/cmH_2O, respectively, for a non-obese patient to inflate 500 mL, pressures of 2.5 and 5 cmH_2O are required to mobilize the chest wall and lungs, respectively. Therefore, 7.5 cmH_2O is the respiratory system driving pressure. In non-obese anesthetized patients, lung injury is believed to initiate when the respiratory system driving pressure exceeds 13 cmH_2O [9], which is equivalent to a transpulmonary driving pressure of 10 cmH_2O. In obese patients, chest wall and lung compliances are on average 100 and 50 mL/cmH_2O, respectively; thus, to inflate the same 500 mL, an obese individual requires pressures of 5 and 10 cmH_2O to mobilize the chest wall and lungs, respectively. Therefore, the difference mainly relies on lung compartment, likely due to its size in obese patients [10]. In order to avoid lung injury, 15 cmH_2O is the highest acceptable respiratory system driving pressure in obese patients on invasive MV [11] (Fig. 21.2). Although the PROBESE trial showed a reduction in driving pressure among patients receiving PEEP of 12 cmH_2O compared with 4 cmH_2O, this did not result in improved clinical outcome in obese patients undergoing elective surgery. Perhaps driving pressure has a relevant prognostic value in obese patients with acute lung diseases, such as acute respiratory distress syndrome requiring MV.

21.3.2 Plateau Pressure

The respiratory system plateau pressure ($Pplat_{,RS}$) reflects the elastic recoil of the respiratory system. It can be also interpreted as the pressure used to distend both the chest wall and lungs. As a consequence, in obese patients, increased $Pplat_{,RS}$ can be a consequence of changes in the chest wall and/or lung. To better understand the

Non-obese subject:
Chest Wall compliance = 200 mL/H_2O
Lung compliance = 100 mL/H_2O

INPUT

V_T=0.500 L
RR = 18 bpm
PEEP = 5 cmH_2O

OUTPUT

$Ppeak_{,RS}$ = 15cmH_2O
$Pplat_{,RS}$ = 12.5cmH_2O
$\Delta P_{,RS}$ = 7.5 cmH_2O
$\Delta P_{,L}$ = 5 cmH_2O
$\Delta P_{,CW}$ = 2.5 cmH_2O
$MP_{,RS}$ = 9.9 J/min

Lung Injury when $\Delta P_{,RS}$ >13cmH_2O
or $MP_{,RS}$ > 17/min

Obese subject:
Chest Wall compliance = 100 mL/H_2O
Lung compliance = 50 mL/H_2O

INPUT

V_T=0.500 L
RR = 18 bpm
PEEP = 5 cmH_2O

OUTPUT

$Ppeak_{,RS}$ = 22.5 cmH_2O
$Pplat_{,RS}$ = 20cmH_2O
$\Delta P_{,RS}$ = 15 cmH_2O
$\Delta P_{,L}$ = 10 cmH_2O
$\Delta P_{,CW}$ = 5 cmH_2O
$MP_{,RS}$ = 13.2 J/min

Lung Injury when $\Delta P_{,RS}$ >15cmH_2O
or $MP_{,RS}$ > 17J/min*

Fig. 21.2 Simulation of input and output ventilatory parameters for non-obese and obese patients. Chest wall ($_{CW}$) and lung ($_L$) compliances of 200 and 100 mL/H_2O, respectively, for a non-obese patient to inflate V_T = 0.5 L, pressures of 2.5 and 5 cmH_2O are required to mobilize the chest wall ($\Delta P_{,CW}$) and lungs ($\Delta P_{,L}$) respectively. Therefore, 7.5 cmH_2O is the respiratory system driving pressure ($\Delta P_{,RS}$), peak airway pressure ($Ppeak_{,RS}$) is 15 cmH_2O, and the respiratory system mechanical power ($MP_{,RS}$) is 9.9 J/min. In non-obese patients under mechanical ventilation, lung injury is more likely when $\Delta P_{,RS}$ and $MP_{,RS}$ are higher than 13 cmH_2O and 17 J/min, respectively. In obese patients, the chest wall and lung compliances are on average 100 and 50 mL/cmH_2O, respectively; thus, to inflate the same V_T = 0.5 L, an obese individual requires pressures $\Delta P_{,CW}$ = 5 cmH_2O and $\Delta P_{,L}$ = 10 cmH_2O. Therefore, the output ventilator variables are $Ppeak_{,RS}$ = 22.5 cmH_2O; $Pplat_{,RS}$ = 20 cmH_2O; $\Delta P_{,RS}$ = 15 cmH_2O;, and $MP_{,RS}$ = 13.2 J/min. Thus, to avoid lung injury, 15 cmH_2O and 17 J/min would be the highest acceptable $\Delta P_{,RS}$ and $MP_{,RS}$ values in obese patients on invasive mechanical ventilation. *This is a simulation for educational purposes; to date, there are no data on the safe threshold of $MP_{,RS}$ in obese patients under mechanical ventilation

increase in $Pplat_{,RS}$, it is important to calculate transpulmonary or transthoracic pressures to understand the mechanical modifications in the lung or chest wall, respectively. To make assumptions about chest wall mechanics based on $Pplat_{,RS}$ can be misleading. For example, conclusions regarding alveolar overdistension due to a decrease in ventilated area as a consequence of atelectasis based on $Pplat_{,RS}$ alone are inaccurate in the obese population.

Nevertheless, some recommendations on how to manage $Pplat_{,RS}$ in obese patients have been made. $Pplat_{,RS}$ should be <20 cmH_2O in obese patients without acute lung diseases [12]. The authors emphasized that the decreased chest wall compliance in these patients may be associated with intra-abdominal pressure (IAP), as estimated by bladder pressure. Thus, the target $Pplat_{,RS}$ could be based on IAP, using the following formula: adjusted $Pplat_{,RS}$ = target $Pplat_{,RS}$ + IAP − 13 $cmH_2O/2$ [13].

21.3.3 Energy and Mechanical Power

V_T and $Pplat_{,RS}$ have been described as simple surrogate measures of strain and stress, respectively. Strain is defined as the ratio between V_T and EELV. Stress is the distending force of the lung and equals transpulmonary pressure. The energy applied to the respiratory system can be computed based on the airway pressure–volume curve, considering that it is linear up to the total lung capacity region. Thus, the airway pressure–volume area generates the energy applied to the respiratory system during one breath cycle. The energy applied to the lungs at each frequency is called mechanical power, which is effectively the energy imparted per minute [14] and has been associated with mortality in critically ill patients [15]: absolute mechanical power = $0.098 \times V_T \times$ respiratory rate$\times(Ppeak_{,aw} - \Delta P/2)$.

The use of mechanical power to guide management may be of particular interest in obese patients because this parameter is dependent on chest wall elastance and is intrinsically altered in obesity. In patients under MV, stress and energy-based ventilator-induced lung injury indicators are influenced by the relative contributions of the chest wall and lung to overall respiratory mechanics in morbidly obese patients [16]. Numerical guidelines for ventilator-induced lung injury risk must consider adjustment for these elastic characteristics in morbid obesity. Trials focusing on controlling mechanical power should also monitor the mechanical properties of the chest wall and IAP during MV of obese patients with ARDS.

21.4 Conclusion

Input and output ventilatory parameters should be carefully controlled and monitored in obese patients under MV, especially in those at high risk of developing respiratory complications. There are new evidence pointing out safe threshold airway pressure, avoidance of some practices, such as bag squeezing maneuvers, and acknowledgement of new derived ventilator parameters, such as energy and mechanical power.

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Weaning the Simple and Complex Patients

22

Tài Pham, Martin Dres, and Rémi Coudroy

22.1 Introduction

Most patients admitted in the intensive care units (ICUs) are treated with a form of artificial ventilation ranging from simple low flow oxygen through nasal cannula to invasive mechanical ventilation (IMV) in a patient deeply sedated, paralyzed, and proned. Since the poliomyelitis epidemics in the 1950s, ventilation management is the hallmark of critical care and a specific area of expertise for intensivists and respiratory therapists. The recent outbreak of SARS-Cov-2, with a surge of patients

T. Pham (✉)
Service de Médecine Intensive-Réanimation, AP-HP, Hôpital de Bicêtre, DMU 4 CORREVE Maladies du Coeur et des Vaisseaux, FHU Sepsis, Groupe de Recherche Clinique CARMAS, Le Kremlin-Bicêtre, France

Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm U1018, Equipe d'Epidémiologie Respiratoire Intégrative, CESP, Villejuif, France
e-mail: tai.pham@aphp.fr

M. Dres
Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France

Service de Médecine Intensive – Réanimation (Département "R3S"), AP-HP. Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France
e-mail: martin.dres@aphp.fr

R. Coudroy
Médecine Intensive Réanimation, Centre Hospitalier Universitaire de Poitiers, Poitiers, France

INSERM CIC 1402, ALIVE Research Group, INSERM, Université de Poitiers, Poitiers, France
e-mail: remi.coudroy@chu-poitiers.fr

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with acute respiratory distress syndrome (ARDS) related to severe COVID-19 highlighted the importance of the appropriate use of IMV. In the pre-COVID era, it was estimated that treatment with IMV in the ICU was increasing each year, and at peaks of the recent COVID pandemic the ventilator demand worldwide further increased [1]. Though often necessary and lifesaving, invasive ventilation causes specific complications and the decision to start ventilation has major consequences on patients' outcomes while avoiding or delaying intubation could also expose patient to detrimental consequences. Duration of patients' exposition to IMV is directly related to the risk of complications and the process leading to successful separation from the ventilator, known as "weaning" is of paramount importance. It was reported that it may reach up to 50% of the total duration of IMV. In this chapter, we will review the definition(s) of weaning and of patients' phenotypes (from simple to more complex). We will detail the pros and cons of the different types of spontaneous breathing tests (SBTs) and propose specific managements in case of SBT failure as well as strategies to avoid reintubation.

22.2 Weaning Definitions and Steps

22.2.1 What Is Weaning, When Does Is Start? (and When Does It End???)

While mechanical ventilation and its consequences got better understood, characterizing the weaning process grew in importance and yet some basic questions are still to be addressed. The weaning process, its steps and success are not perfectly defined, and the lack of consensual definitions is a source of uncertainty and confusion.

In 2007, a task force gathering experts from five major scientific societies published the statement of a consensus conference focusing on weaning [2]. This valuable contribution helped clarifying many points as authors proposed definitions for weaning success and failure and proposed a classification according to the weaning process (Table 22.1) suggesting strategies to avoid weaning failure. However, several important flaws limited its spread use and only a small number of subsequent studies used the consensus definitions [3], often modifying it to make it applicable [3]. Trying to address these limitations, Béduneau and colleagues performed an observational study on 2729 patients receiving IMV and proposed different definitions and classification. In this cohort, authors introduced the concept of separation attempt, that allowed to classify all patients receiving IMV (Table 22.1) [4]. In contrast, the consensus conference definitions failed at classifying almost half of the patients from this cohort. Nonetheless, the WIND definition is not perfect: patients are retrospectively grouped when the weaning processed is over and weaning termination considers a duration as opposed to a patient centered outcome: termination could be weaning success or death (which is very different from a patient perspective). Nevertheless, several studies used the WIND definitions [5, 6] and showed its superiority over the consensus conference definitions in terms of applicability and mortality separation between groups [6].

Table 22.1 Consensus conference and WIND definitions

Consensus conference definitions	
Spontaneous Breathing Trial (SBT)	T-tube trial or a low-level pressure support (≤8 cmH_2O)
SBT failure	Objective indices (tachypnea, tachycardia, hypertension, hypotension, hypoxemia, acidosis, arrhythmia) Subjective indices: agitation, distress, depressed mental status, diaphoresis, increasing effort
Weaning success	Extubation without ventilatory support 48 h following the extubation
Weaning failure	Failed SBT or reintubation and/or resumption of ventilatory support or death within 48 h following extubation
Weaning in progress	Extubation with the need of NIV
Simple weaning	Patients who proceed from initiation of weaning to successful extubation on the first attempt without difficulty
Difficult weaning	Patients who fail initial weaning and require up to three SBT or as long as 7 days from the first SBT to achieve successful weaning
Prolonged weaning	Patients who fail at least three weaning attempts or require >7 days of weaning after the first SBT
WIND definitions	
Separation attempt	For intubated patients: a SBT with or without extubation, or an extubation directly performed without identified SBT (whatever the type: planned or unplanned extubation) For tracheostomized patients: 24 h or more with spontaneous ventilation through tracheostomy without any mechanical ventilation.
Successful weaning or separation	For intubated patients: extubation without death or reintubation within the next 7 days whether postextubation noninvasive ventilation (NIV) was used or not, or ICU discharge without invasive mechanical ventilation within 7 days, whichever comes first For tracheostomized patients: spontaneous ventilation through tracheostomy without any mechanical ventilation during 7 consecutive days or discharged with spontaneous breathing, whichever comes first
Group "no weaning"	Patients who never experienced any separation attempt
Group 1 (short weaning)	The first attempt resulted in a termination of the weaning process within 1 day (successful separation or early death)
Group 2 (difficult weaning)	The weaning was completed after more than 1 day but in less than 1 week after the first separation attempt (successful separation or death)
Group 3 (prolonged weaning)	Weaning was still not terminated 7 days after the first separation attempt (by successful separation or death)

Considering these definitions issues, it is quite challenging to provide a clear answer to the question "when does weaning start?" because, for a given patient, different clinicians will consider weaning process begins at a different moment of the course of mechanical ventilation. Different landmark events could be considered as the beginning of the weaning process: (1) sedation decrease; (2) sedation weaning; (3) ventilator support reduction (lowering FiO_2, positive end-expiratory pressure

[PEEP], (4) hypoxemia improvement; (5) evidence of spontaneous breathing whatever the mode of ventilation; (6) ventilator switch to an assisted mode; (7) a SBT (Fig. 22.1).

There is no right or wrong answer and all these key events are important in the process leading to separating the patient from the mechanical ventilation. The international observational WEAN SAFE study (WorldwidE AssessmeNt of Separation of pAtients From ventilatory assistance) will provide granular data on the daily patients' management during IMV, particularly the marking events during the weaning phase (NCT03255109, www.esicm.org/trials-group-2/wean-safe/).

Weaning termination is also still a matter of debate and discussions regarding its definition are explored in the dedicated section "extubation failure" below.

22.2.2 Are There Simple and Complex Patients?

Different weaning approaches and challenges arise depending on the patient's phenotype. Though each patient is a specific individual, categorizing two different groups namely "simple" and "complex" can help defining broad management and distinct goals. On one hand, intensivists should not delay weaning in a "simple patient" with high chances of early successful weaning and on the other hand, they should ideally be able to identify as early as possible when a more "complex patient" is eventually ready to be weaned. Typically, a "simple" patient is a young patient (<65 y.o) not presenting significant, cardiac or respiratory past medical history receiving mechanical ventilation for a rapidly resolving cause (e.g. toxic coma, surgery). Prolonging mechanical ventilation in such a patient could lead to undue complications such as sedation side effects, ventilation acquired pneumonia or self-extubation. In these patients, extubation could even be performed without a SBT, especially when they have not been ventilated for more than 24–48 h. On the

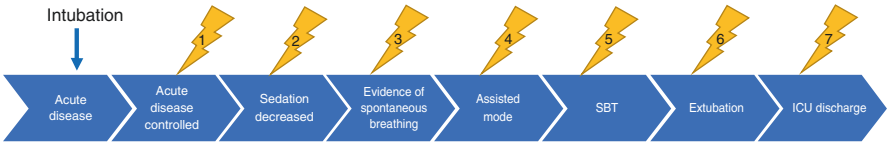

Fig. 22.1 Landmark events in the evolution of a patient receiving mechanical ventilation and adverse events that could occur during the ICU stay

At any time point during the course of mechanical ventilation, intercurrent event or complication can occur:

- Need for going back to the previous step (sedation increase, switch to a controlled mode, etc.)
- Accidental or self extubation (1, 2, 3, 4, 5)
- Ventilation acquired pneumonia or new acute disease (1, 2, 3, 4, 5)
- SBT failure (6)
- Reintubation (6, 7)
- Post-extubation respiratory distress (6)
- ICU readmission (7)
- Tracheostomy (1, 2, 3, 4, 5)
- Death (1, 2, 3, 4, 5, 6, 7)

contrary, complex patients can raise specific challenges and each step of the management in the ICU will impact timing as well as outcomes of weaning. Patients with the ARDS [7], those with severe congestive heart failure or chronic obstructive pulmonary disease typically belong to this category of "complex" patients. Patients with COVID-19 related ARDS had longer durations of IMV than other ARDS patients [8–10], undoubtedly belonging to the "complex patient group." However, there is no strong evidence to use a different approach for weaning in this specific group of patients (see also Chap. 24). Finally, patients with neurologic failure or traumatic brain injury constitute a specific group whose weaning can be challenging due to cough or secretion clearance issues and sometimes require airway protection with a tracheostomy without requiring mechanical ventilation per se.

22.2.3 During the Acute Phase

As soon as a patient is intubated, the team in charge should think of the strategies available aiming at keeping the total duration of ventilation as short as possible to limit complications related to ventilation exposure. Thus, practice guidelines recommend using protocols aiming at keeping sedation as minimal as possible and to consider protocolized rehabilitation directed toward early mobilization [11, 12]. Lung protective ventilation using controlled modes with low tidal volume, limiting driving pressure and for the most hypoxemic patients' treatment with paralysis and prone position has been broadly adopted worldwide. However, this approach keeping the patients passive could delay weaning and favor muscle disuse. Recently, experts brought forward the concept of "lung and diaphragm" protective ventilation: a tradeoff balancing VILI and Ventilator-induced diaphragm dysfunction by monitoring respiratory muscles, maintaining not excessive respiratory effort and minimizing dyssynchrony [13]. The concept of lung and diaphragm protective ventilation is seducing and logical but has not demonstrated its benefits yet. Several studies are currently in progress (NCT03527797; NCT03612583; NCT03646266).

22.2.4 After the Illness Acute Phase

When the initial acute illness is controlled, clinicians should aim at separating the patient from the ventilator as early (and as safely) as possible. During this period, the ventilator is usually switched from an assist-control to a partially supported mode allowing patient effort. Several modes are available (pressure support ventilation [PSV], proportional assist ventilation, neurally adjusted ventilator assist, etc.) as discussed in dedicated sections of this book, but PSV is the most used worldwide [5]. There is no proof that one mode is superior to the other ones but once on supported mode, physicians should optimize ventilation settings to provide minimal support keeping the patient comfortable. This requires multiple assessment per day and there is evidence that ventilator liberation protocols led by nurses, respiratory therapists or even computer driven hasten the process getting to weaning readiness and the realization of a SBT [14, 15]. There is no consensus regarding the weaning readiness

criteria that should prompt a SBT but we propose the following list as a reasonable prerequisite: presenting spontaneous breathing efforts, $FiO_2 \leq 0.5$, PEEP$\leq$10 cmH_2O, $PaO_2/FiO_2 > 200$ mmHg, not receiving vasopressors or receiving low doses of vasopressors (less than 0.2 μg/kg/min of norepinephrine or equivalent). The use of the rapid shallow breathing index (disconnecting the patient from the ventilator over 1 min) can be useful to identify patients capable to undergo a SBT [16].

In the future, artificial intelligence and machine learning able to integrate an important amount of data readily available might also be helpful to facilitate the weaning process.

22.3 The Separation Attempt Process

22.3.1 Challenges and Pitfalls

When the acute phase is controlled and patient's respiratory and hemodynamics status seem appropriate (cf. weaning readiness criteria above), a SBT is usually performed before extubation [2, 4, 5, 17]. The SBT is a test challenging ability to breathe without any ventilator assistance. If the patient passes SBT, extubation should be considered but successful SBT is actually not always followed by extubation [4]. This is not surprizing since readiness to breathe without assistance does not necessary imply readiness for extubation which requires appropriate awareness, cough strength, and no risk of glottis patency.

Observational studies show that SBTs are not consistently used in routine [4, 5]. In the above-mentioned WIND cohort, 12% of the patients (with no withholding/withdrawal decisions) were extubated without previous SBT [4] and 28% of the patients from a recent international epidemiological study had direct extubation without SBT [5]. However, both strategies (extubation with or without a SBT) were associated with similar outcomes [4, 5]. SBT relevance is therefore questionable particularly for the patients at low risk of extubation failure. First, the SBT could generate anxiety, air hunger, and dyspnea which are poorly detected by caregivers [18]. Second, inter-observer disagreement on the outcome of the SBT may lead to misinterpretation and delayed extubation. Third, even a successful SBT is followed by extubation only in 58% of the patients [4]. Therefore, when the pre-test probability of failure is low (as in the majority of the patients entering into the weaning process), performing a SBT may delay extubation [19]. The sensitivity and specificity of SBT for predicting successful extubation are difficult to estimate. The extubation failure rate is around 15%, which makes the specificity of the test for predicting successful extubation 85% [17]. By contrast, the proportion of patients able to tolerate extubation despite failing the SBT (i.e., false-negative test results, used to determine sensitivity) is not easy to evaluate because patients who fail a SBT are usually not extubated. However, among patients who self-extubate (independently of readiness to wean criteria), only 40–60% require reintubation [20]. Moreover, in a trial studying extubation outcomes in patients who failed a SBT, 42% of the patients did not require rescue noninvasive ventilation to treat post-extubation respiratory failure and only 37% were reintubated [21]. Judgment of

the SBT tolerance relies on objective criteria [2] but also depends on the clinician's skills, and erroneous decision can have deleterious consequences for the patients.

22.3.2 Which Spontaneous Breathing Trial?

Many modalities of SBT were described but T-piece or PSV with no PEEP and a support level of 0 cmH_2O seem to best reflect the work of spontaneous breathing without assistance (Table 22.2) [22]. These two tests might be more challenging and "physiologically demanding" than other tests, however, they are not more "demanding" than extubation itself [22]. In the above mentioned WIND study, half of the SBTs were conducted either with minimal pressure support with/without PEEP (42%) or T-piece (40%) [4] but in a recent international study, initial SBTs most commonly used PSV with PEEP (49%) or T-piece (25%) and less frequently applied CPAP (11%) or PSV without PEEP (9%) [5]. Does the modality of SBT influence the outcome of the patients? The most recent meta-analysis included ten randomized clinical trials (3165 patients) and showed that T-piece and minimal pressure support (with/without PEEP) have comparable performance to predict successful extubation in critically ill patients [22]. The largest randomized controlled trial (included in this meta-analysis) included 1153 patients and compared a SBT of 30 min of PSV to a more challenging 2-h T-piece SBT and showed a higher successful extubation rate (82% vs. 74%) favoring the shortest test [19]. These findings confirm that PSV trial is easier to pass than T-piece trial and may hasten extubation

Table 22.2 Characteristics of the main types of spontaneous breathing trials

	T-tube	Pressure support	Pressure support 0, PEEP 0
Method	• Disconnection from the ventilator • Oxygen can be administered directly to the endotracheal tube (or the tracheostomy)	• Patient connected to the ventilator • Low level of pressure support +/− PEEP • Sometimes PEEP alone	• Patient connected to the ventilator • No ventilatory assistance
Rational	• To mimic "post-extubation" respiratory conditions	• To compensate breathing through a ventilator circuit	• To mimic "post-extubation" respiratory conditions
Advantages	• Standardizsation	• No need for circuit disconnection • Monitoring of breathing pattern	• Standardizsation • Monitoring of breathing pattern
Disadvantages	• No breathing pattern monitoring • Uncertainty of FiO_2	• Practice heterogeneity (pressure support and PEEP combinations, depend on ventilator brand)	• No clinical results available

FiO_2 oxygen inspired fraction, *PEEP* positive end expiratory pressure

without an increased risk of reintubation. However, in this study, the proportion of patients with simple weaning (high pre-test probability of success) was particularly high, thereby limiting generalizability. No test is perfect, and the risks of false negatives or false positives always exist. As already stated, the predictive value of a test very strongly depends on the pre-test probability and therefore on the characteristics of the population tested. In a population selected by the failure of a first or further separation attempts, it makes sense to use more challenging tests such as T-piece (or on the ventilator without ventilatory support) to avoid underestimation of a potential next failure. Likewise, in patients at high risk of extubation failure, performing an initial SBT using T-piece could avoid inappropriate extubation. However, this hypothesis was not confirmed in a post-hoc analysis of a multicenter trial [23].

22.3.3 Pathophysiology of Spontaneous Breathing Trial Failure

SBT failure occurs in case of respiratory capacity/load imbalance. Increased work of breathing due to airway resistance is frequent in patients with chronic obstructive pulmonary disease [16], which explains the high prevalence of SBT failure in this population. Increased airway resistance leads to intrinsic positive end-expiratory pressure (PEEPi) in particular with a reduced expiratory time when a patient develops a rapid breathing pattern [16]. Figure 22.2 displays the main physiological mechanisms potentially leading to weaning induced pulmonary edema, a frequent cause of SBT failure. Echocardiography is likely the best tool to diagnose weaning induced cardiogenic pulmonary edema [24]. A normal left ventricle ejection fraction does not prevent weaning induced cardiac dysfunction because left ventricle diastolic function plays a major role [25]. The diagnosis of weaning induced cardiac edema can also be done by measuring the filtration of fluid from the vascular compartment toward the alveoli and the interstitium [26]. This transfer of fluid induces a plasma volume contraction that can be evidenced by an increase in plasma protein concentration (or hematocrit) higher than 5–6% between the beginning and the end of the SBT [27]. The treatment of weaning induced cardiac dysfunction (and pulmonary edema) mainly relies on fluid removal and antihypertension drugs (rather than inotropes). Changes in lung and/or chest wall compliance induced by pleural effusion may also be involved in case of weaning failure but this remains controversial [28].

The capacity of the respiratory system may be reduced in case of decreased respiratory muscles force and/or decreased respiratory drive. Impaired respiratory drive is an obvious cause of weaning failure frequently observed in patients with stroke, central hypoventilation, and metabolic alkalosis. Another frequent reason for a decreased respiratory drive is simply the use of sedatives that are not always (or insufficiently) interrupted or cleared at the time of weaning especially in case of renal failure. Critical illness polyneuropathy and myopathy are frequently observed in patients who fail the SBT and coexist with respiratory muscle weakness [29]. The high prevalence of diaphragm dysfunction at the time of weaning (two thirds of the patients) could participate to weaning failure. Nevertheless, some patients pass the SBT and are successfully extubated despite diaphragm dysfunction [29, 30]. Therefore, it is of paramount importance to rule out other reasons of failure

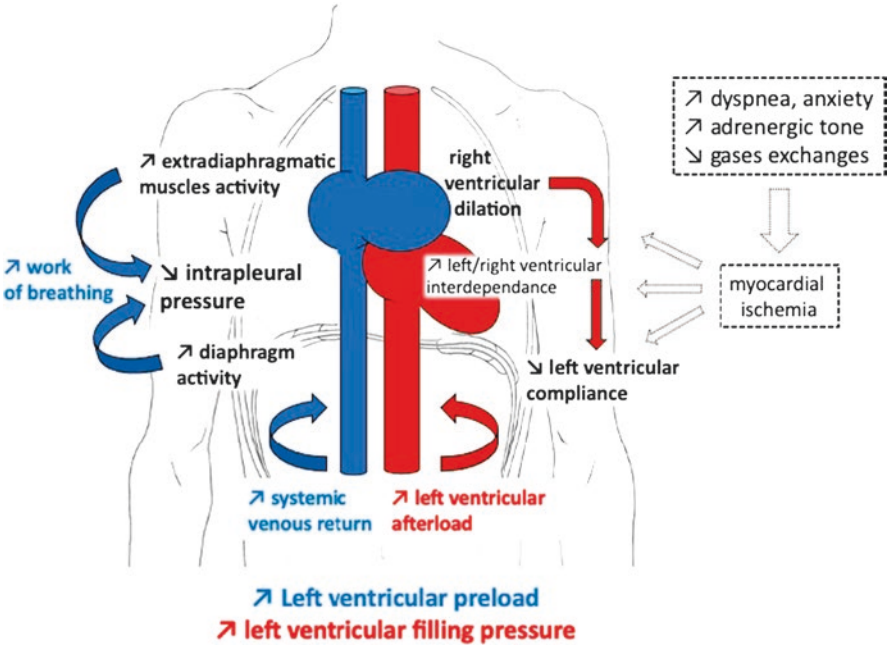

Fig. 22.2 Mechanisms leading to weaning induced pulmonary oedema (WIPO). Given the close interaction between the cardiovascular function and the respiratory system, all these mechanisms may be exacerbated in a patient with chronic obstructive pulmonary disease. The main trigger is the decrease in intrathoracic pressure induced by the switch from mechanical ventilation (positive intrathoracic pressure) toward spontaneous breathing (negative intrathoracic pressure). The consequence is an increase in venous return that could lead to right ventricle dilation and right/left ventricles interdependence. The decrease in intrathoracic pressure also generates an increase in left ventricle afterload (the left ventricle has to overcome the decrease in intrathoracic pressure before to eject the blood outside the thorax). In addition, myocardial ischemia can also occur and may worsen the left ventricle function. All these mechanisms, are susceptible to induce a weaning induced cardiac dysfunction leading to pulmonary edema and to spontaneous breathing trial failure (79). Source: Dres, M., Rozenberg, E., Morawiec, E. et al. Diaphragm dysfunction, lung aeration loss and weaning-induced pulmonary oedema in difficult-to-wean patients. Ann. Intensive Care 11, 99 (2021)

(especially weaning induced cardiac edema) before incriminating diaphragm dysfunction as the main cause of weaning failure.

22.4 Preventing Extubation Failure

22.4.1 Complications Following Extubation: Epidemiology and Definitions

Affecting 25% of the patients, post-extubation respiratory failure is the most frequent complication after planned extubation [31–33]. Although its definition is not consensual, it is often characterized by increased respiratory rate and other clinical signs suggesting respiratory distress, hypoxemia, or respiratory acidosis [31–33].

From 45 to 80% of patients with post-extubation respiratory failure experience subsequent reintubation [34]. Criteria for reintubation are heterogeneous but parallel those used to define post-extubation respiratory failure: increased respiratory rate, clinical signs suggesting respiratory distress, hypoxemia or respiratory acidosis [34]. The timing of reintubation which highlights extubation failure is also debated, ranging from 48 h to 7 days after extubation. Consequences of reintubation include prolonged duration of mechanical ventilation but also increased mortality ranging from 25 to 50% [3, 20]. Given this increased risk of death and the small number of patients reintubated later than 1 week after extubation, most of studies defined extubation failure by the need for reintubation within the first 7 days following planned extubation [4, 33].

22.4.2 Risk Factors of Extubation Failure

The risk of extubation failure is not similar for all patients and most studies comparing strategies to prevent it stratified patients according to their pre-extubation level of risk.

Many factors associated with increased risk of reintubation have been identified. Some were related to the patient's characteristics such as age, obesity, and comorbidities, especially underlying cardiac or lung disease [20, 31]. Others were related to the acute illness such as the reason for intubation, positive cumulative fluid balance, dysfunction of respiratory muscles assessed using magnetic phrenic stimulation, diaphragm ultrasound or their surrogates, weak cough and the amount of secretions, ICU-acquired weakness, prolonged duration of mechanical ventilation or elevated severity score on the day of extubation. Whereas others pertained to the SBT itself such as one or more failed SBT, high rapid shallow breathing index, or were even assessed after extubation such as upper airways stridor at extubation or dyspnea.

However, considering all these risk factors may lead to erroneously classify all ICU patients at high risk and to propose inappropriate strategy to prevent extubation failure. A pragmatic approach could be to consider patients at high risk if they present one of the three following characteristics: older than 65 years and/or underlying cardiac and/or chronic respiratory disease. According to the original observational cohort study in which these easy-to-assess criteria have been identified, patients at high risk of extubation failure have a reintubation rate of 28%, whereas patients at low risk have a reintubation rate of 10% [35].

22.4.3 Strategies Aiming at Preventing Extubation Failure

Post-extubation respiratory failure is the main cause of reintubation [36]. Therefore, strategies to prevent extubation failure aimed at reducing work of breathing and normalizing gas exchanges. Several oxygenation strategies are available in the post-extubation period comprising conventional oxygen therapy, noninvasive ventilation, and high-flow nasal oxygen therapy.

Noninvasive ventilation delivers positive pressure ventilation in the airways through a sealed mask avoiding leaks. During expiration, airway pressure remains positive, increasing end-expiratory lung volume, and oxygenation. During inspiration, an additional pressure support allows to decrease respiratory rate and the work of breathing.

High-flow nasal oxygen therapy delivers heated and humidified mixture of air and oxygen through nasal cannulas. It can provide high inspired fraction of oxygen, close to 100% with flow rate reaching 60 L/min. In patients with acute hypoxemic respiratory failure, high-flow nasal oxygen therapy increased end-expiratory lung volume and oxygenation, while reducing respiratory rate and work of breathing [37].

22.4.4 Summary of the Evidence Regarding the Efficacy of Strategies Aiming at Preventing Extubation Failure in the ICU

Results from the clinical trials comparing the different strategies to prevent reintubation are summarized in the e-Table 1. Although the definition of high risk of extubation failure was heterogeneous, results of the different studies were consistent.

In unselected patients, neither noninvasive ventilation nor high-flow oxygen therapy were associated with lower rate of reintubation as compared to standard oxygen (14% vs. 9%, and 10% vs. 13%, respectively). For this reason, the international clinical practice guidelines do not support the use of noninvasive ventilation to prevent extubation failure in unselected patients [38].

In patients at low risk of extubation failure, high-flow oxygen therapy was associated with lower rate of reintubation as compared to standard oxygen therapy (5% vs. 14%, overall) (e-Table 1). Surprisingly, reintubation rates in control groups treated with conventional oxygen therapy were much higher than the 10% expected.

In patients at high risk of extubation failure, noninvasive ventilation was associated with lower rates of reintubation as compared to conventional oxygen therapy (10% vs. 22%) and to high-flow oxygen therapy (14% vs. 19%). The only trial comparing high-flow nasal oxygen therapy to conventional oxygen therapy did not find any difference in reintubation rate (e-Table 1). These findings led the international clinical practice guidelines to recommend the use of noninvasive ventilation in patients at high risk of extubation failure to prevent extubation failure [38].

22.4.5 Treatment of Post-Extubation Respiratory Failure

In a randomized trial including 221 patients with post-extubation respiratory failure, noninvasive ventilation was not associated with lower reintubation rate as compared to conventional oxygen therapy (48% in both groups) [39]. However, mortality rate in the noninvasive ventilation group was higher than in the conventional oxygen therapy group (25% vs. 14%, $p = 0.048$) [39]. The main hypothesis explaining this

result was the longer time to reintubation in patients treated with noninvasive ventilation (12 h vs. 2 h 30, $p = 0.02$) [39]. Such harm was not found in another randomized trial comparing noninvasive ventilation to conventional oxygen therapy in 81 patients with post-extubation respiratory failure [40]. Moreover, a post-hoc analysis of a randomized trial including 146 patients with post-extubation respiratory failure suggested that noninvasive ventilation was not harmful as compared to high-flow oxygen therapy, and could even benefit to the subgroup of patients with hypercapnia [34].

Therefore, although the international clinical practice guidelines recommend against the use of noninvasive ventilation to treat post-extubation respiratory failure in unselected patients [38], specific subgroups might benefit from this technique, leaving the question of the treatment of post-extubation respiratory failure unresolved.

22.5 Conclusion

The weaning phase is a key period that can account for an important part of the total duration of mechanical ventilation. The "simple" patients should be identified and extubated as early as possible (sometimes without SBT) to avoid adverse events associated with delayed weaning. Strategies to facilitate weaning of "complex patients" should be implemented as soon as the patient is intubated and optimized throughout the course of mechanical ventilation.

The mode of mechanical ventilation used at the different steps could impact weaning but there is no proof of the superiority of a mode over the others. When general weaning readiness criteria are fulfilled, a SBT can help predicting the extubation outcomes but the most appropriate type of SBT is still debated. Finally, noninvasive ventilation or humidified high-flow oxygen canulae could prevent extubation failure in specific subgroup of patients.

Despite being of paramount importance for all patients receiving mechanical ventilation, the weaning process is not fully understood yet. Future consensus and research on each step of the weaning process might better delineate the weaning phase and provide answers to all these remaining questions.

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Non-invasive Oxygenation Strategies for COVID-19 Related Respiratory Failure

23

Michael C. Sklar, Bhakti K. Patel, and Laveena Munshi

23.1 Introduction

On March 11, 2020, The World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic [1]. Since that time, tens of thousands of patients with COVID-19 have presented to hospital with severe acute respiratory failure requiring admission to intensive care units (ICU). This volume of patients rapidly overwhelmed some jurisdictions as critically-ill patients began to outstrip the limited critical care resources. Triage protocols, non-invasive support strategies, and interventions to manage patients on the hospital wards were developed during this time of crisis. One such strategy was the use of non-invasive oxygen devices such as high-flow nasal cannula and face mask and helmet non-invasive ventilation. Utilization of non-invasive devices was initially met with trepidation in some

M. C. Sklar
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Anesthesia and Pain Medicine, St. Michael's Hospital, Unity Health Toronto and University of Toronto, Toronto, ON, Canada

B. K. Patel
Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, IL, USA

L. Munshi (✉)
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Medicine, Sinai Health System and University Health Network, Toronto, ON, Canada

Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
e-mail: Laveena.munshi@sinaihealth.ca

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centers given the uncertainty about its safety for patients and health care providers (aerosols) or its effectiveness. However, where ventilators were limited in number, these devices were adopted out of necessity. The ventilator-sparing potential of these non-invasive oxygenation strategies for patients with COVID-19 has inspired much research. Chapter (10) and chapter (9) describe the application of high-flow nasal oxygen and non-invasive positive pressure ventilation. In this chapter we outline unique considerations surrounding the use of these devices during a global respiratory pandemic and evaluate their effectiveness in COVID-19 respiratory failure.

23.2 Non-invasive Oxygen Strategies: Devices, Physiology and Non-COVID-19 Evidence

23.2.1 Devices and Physiology

Non-invasive oxygenation strategies can be delivered by conventional non-invasive ventilation (NIV) via a face-mask interface, NIV via a helmet interface, or high-flow nasal cannula (HFNC). Each of these techniques has unique physiological considerations and important advantages and disadvantages that must be understood to deliver safe, effective, and personalized therapy (Table 23.1). Matching the appropriate patient and clinical condition to a non-invasive oxygen strategy is imperative to derive optimal benefit.

Table 23.1 Advantages and disadvantages of common non-invasive oxygen devices

Device	Advantages	Disadvantages
Non-invasive face mask	Pressure support to improve alveolar ventilation PEEP to improve oxygenation Can improve cardiac function through decreasing preload and afterload Can monitor high tidal volumes	Possible aerosolization Risk of skin ulceration Air leaks limiting higher PEEP Long duration may not be tolerated Risk of high tidal volumes or patient self-inflicted lung injury Challenges with transportation
Non-invasive helmet	Pressure support to improve alveolar ventilation Allows for higher PEEP than face-mask NIV to improve oxygenation Greater tolerance allowing for longer durations of therapy	Cannot measure tidal volume In the event of an airway emergency, may take longer to remove device Less familiarity compared to face-mask NIV at many institutions Transport difficult
High-flow nasal oxygen	Comfortable and well tolerated Heated and humidified oxygen enhances mucociliary clearance Possible small amounts of PEEP generation Decreased entrainment of room air Dead-space washout Decreased work of breathing	Possible aerosolization Transport challenges PEEP generation is minimal at best Higher flows may be uncomfortable Heated humidification may not be tolerated

NIV non-invasive ventilation, *PEEP* positive end-expiratory pressure

23.2.1.1 High-flow Nasal Oxygen Cannula

HHFNC delivers high flows of humidified oxygen via a specialized nasal cannula interface. The device is connected to an air-oxygen blender that allows for independent titration of the fraction of inspired oxygen (Fio_2) and flow [2]. The system allows for delivery of gas flow up to 60 L/min (some devices allow even higher flows) with an FiO_2 of up to a 100%. These flow rates have the advantage of potentially matching flows of severely dyspneic patients, thereby preventing entrainment of room air and dilution of delivered oxygen [3]. Other proposed physiological benefits of HFNC include dead-space washout, decreased work of breathing, and improved end-expiratory lung volume. These may mitigate the risk of lung and diaphragmatic injury [3, 4]. Furthermore, the humidification may enhance mucociliary clearance of secretions and prevent cold-air induced bronchospasm. For more details on HFNC, please refer to Chapter (XX).

23.2.1.2 Non-invasive Ventilation

In patients with acute respiratory failure, NIV is often delivered by application of a full oro-nasal facemask. Additional NIV interfaces include a helmet apparatus, which has garnered much attention in recent years [5]. NIV is delivered through bi-level positive airway pressure with inspiratory positive airway pressure (IPAP) and end-expiratory pressure (EPAP), similar to PEEP [6]. Physiologically, NIV increases airway pressure, improves arterial oxygenation, increases end-expiratory lung volume, and decreases the intrapulmonary shunt and expiratory diaphragm loading. NIV may also improve cardiac performance by reducing left ventricular afterload and right and left ventricular preload [6, 7]. NIV delivered through a helmet has similar physiological benefits as face-mask NIV, but has the advantage of minimizing substantial leak with a soft collar neck seal. This may result in more effective recruitment and enhanced PEEP titration. Furthermore, helmet NIV may be better tolerated, allowing for longer duration of NIV therapy. For more details on NIV, please refer to Chapter (XX).

23.2.1.3 Evidence of Non-invasive Oxygen Strategies for De Novo Acute Respiratory Failure

The optimal non-invasive oxygenation strategy for de-novo acute respiratory failure remains unknown. This may be due, in part, to the heterogeneous nature of respiratory failure and increasing recognition of subphenotypes [8]. In clinical practice, it is likely that there is a differential treatment response to different non-invasive modalities depending upon the cause of respiratory failure, severity of illness, and time course of their disease.

The use of HFNC rapidly increased following the publication of the FLORALI trial [9]. This three-arm randomized controlled trial compared standard face-mask oxygen to HFNC and face-mask NIV in 313 patients with hypoxemic respiratory failure. It demonstrated a significant reduction in 90-day mortality with the use of HFNC compared to the other modalities. The hazard ratio for death at 90 days was 2.01 (95% confidence interval [CI], 1.01 to 3.99) with standard oxygen versus HFNC ($P = 0.046$) and 2.50 (95% CI, 1.31–4.78) with NIV versus

HFNC ($P = 0.006$). High tidal volumes on NIV were theorized to have contributed to the higher mortality seen across those receiving NIV compared to HFNC.

A recent network meta-analysis comparing all non-invasive oxygen modalities found a significantly lower odds of endotracheal intubation and death with face-mask NIV (RR, 0.76, 95% CI 0.62–0.90—intubation; RR, 0.83, 95%CI 0.68–0.99—death) compared to conventional oxygen therapy [10]. However, the mortality benefit of face-mask NIV was no longer present in the subgroup analysis of patients with more severe respiratory failure (mean PaO_2/FiO_2 <200). In this same network meta-analysis, helmet NIV was also associated with a lower risk of intubation (RR, 0.26 (95%CI 0.14–0.45)) and mortality (RR, 0.40 (95%CI 0.24–0.63)) compared to conventional oxygen therapy [10]. Interestingly, the mortality and intubation benefit of helmet NIV was also seen compared to other modalities (HFNC and face-mask NIV). This analysis was limited by a small number of studies.

23.3 Considerations for Non-invasive Oxygenation Strategies in the COVID-19 Pandemic

The escalation of the COVID-19 pandemic and subsequent surge in patients highlighted important considerations surrounding the role of non-invasive oxygen strategies. Centers that were overwhelmed with high volumes of patients looked to these devices for their ventilator-sparing potential. In contrast centers without capacity issues had an initial reservation to their use given (1) anecdotal reports of benefits "early intubation" and (2) uncertainty regarding the risks of aerosolization. Once it became clear that COVID-19 respiratory failure should be managed in accordance with the same principles of management prior to the pandemic (i.e. no standard "early intubation"), centers began to evaluate the safety, feasibility, and efficacy of non-invasive oxygen devices for patients with COVID-19. The unique considerations for the use of non-invasive oxygen devices during a pandemic are highlighted in this section and in Table 23.2.

Table 23.2 Unique considerations for the use of non-invasive oxygen strategies during a respiratory pandemic

Be aware of hospital oxygen supply: identify what is the highest number of HFNC devices that can be simultaneously operated
Develop protocols on how to care for critically-ill patients in non-traditional ICU settings
Training may be required for additional staff to partake in care of critically-ill patients in these non-traditional spaces (i.e. post-operative recovery health care workers)
Enhanced personal-protective equipment for health care workers managing patients on non-invasive oxygen devices
Be aware of the risks of viral particle aerosolization according to the device under use. Apply appropriate protective measures based upon the characteristics of the virus and impact of the device (e.g. N95, negative pressure rooms if needed)
Develop a strategy on how to transport of critically-ill patients requiring non-invasive oxygen support (e.g. transition trial to Tavish face mask, transport using medical face mask over device)

23.3.1 Caring for Critically-Ill Patients Outside of the Intensive Care Unit

Typically, non-invasive oxygen devices are used predominantly in ICU settings. However, due to limitations in critical care capacity during the pandemic, many hospitals developed strategies for their use outside of the ICU.

HFNC has increasingly been used for severe COVID-19 pneumonia on general medical wards [11]. Two important considerations include (1) having a sufficient supply of oxygen in the hospital and (2) accurately identifying patients at higher risk of HFNC failure. Given the high flows required for HFNC, there were reports of hospitals running out of oxygen when a high number of devices were being used. It is imperative that hospital leaders meet with hospital engineers to establish in advance, the maximum number of devices that could be run simultaneously during a respiratory pandemic.

In an ideal setting, patients on HFNC should be admitted to an environment with close monitoring. Inadvertent disconnection or progressive hypoxia despite HFNC may lead to profound and rapid desaturation. However, due to resource limitations, it was not always feasible to administer HFNC in an ICU setting. Strategies adopted during the pandemic ranged from (1) dedicated HFNC wards for patients with do-not-intubate orders, (2) dedicated HFNC high intensity units where the nursing/respiratory therapy ratios were higher than a general ward but lower than an ICU, (3) admitting lower risk patients to general wards with continuous pulse oximetry and video surveillance, and/or (4) developing thresholds based upon serially measured flow rates, oxygen, PaO_2/FiO_2 or independent scoring systems to prompt ICU admission decisions. Accurately assessing patients at risk for HFNC failure was of prime importance to identify patients who may urgently require invasive mechanical ventilation. Pre COVID-19, the ROX index (defined as the ratio of pulse oximetry/fraction of inspired oxygen (SpO_2/FiO_2) to respiratory rate RR) was developed to identify those at risk of HFNC failure [12]. Across a pre-COVID population, a ROX index of <4.88 at 12 h was associated with a higher risk of HFNC failure. The ROX index was evaluated in a recent study of 120 patients with COVID-19 receiving HFNC [13]. A 12-h ROX index threshold of <5.99 was associated with a higher risk of failure [Specificity 96% Sensitivity 62%]. In a retrospective analysis of 164 patients with COVID-19 supported by HFNC, ROX index (using the traditional cut off) was used to predict HFNC success with a sensitivity of 85% [14]. The application of NIV should be restricted to units (ICUs or high dependency units) close monitoring given the need for expertise in NIV titration, recognition of failure and skillset to intubate.

23.3.2 The Risk of Aerosolization

Since the start of the pandemic, there was a significant concern about the risk of aerosol generation from HFNC and NIV. There have been several simulation studies to define aerosolization risk for these devices. One simulation study involved 8

healthy volunteers placed in emergency department rooms that were positive-pressure ventilated with one room exchange of air every 10 min [15]. Subjects were placed on nonrebreather masks, HFNC (at 15, 30, and 60 L/min) and face-mask CPAP of 10 cm H_20. Both nonrebreather mask and HFNC were performed with and without a surgical mask on subjects. Investigators found that increasing flow rates of HFNC compared to both CPAP and nonrebreather mask use was associated with significantly greater aerosol generation. However, the HFNC-related aerosol generation was reduced when a surgical mask was placed over the subject, as has been described by other groups [16]. In an ICU simulation study measuring particle counts at various positions in the patient room, investigators tested invasive ventilation (through an endotracheal tube with an inflated cuff connected to a mechanical ventilator), helmet NIV, face-mask NIV, nonrebreather face masks, HFNC, and nasal prongs [17]. Closed system ventilation: i.e., invasive ventilation and helmet NIV were associated with the lowest aerosol counts, while HFNC and nasal prongs were associated with the highest. However, in a study of patients with COVID-19, ($n = 7$ on conventional oxygen, $n = 10$ on HFNC) treated in negative pressure rooms, HFNC was not found to increase aerosolization rates as compared to conventional oxygen therapy [18].

While there is conflicting data on the risk of aerosolization, healthcare workers should exercise caution when managing patients with COVID-19 and follow local hospital guidelines. At many institutions, it is recommended that healthcare workers wear a gown, gloves, N-95 respirator, and a face shield when managing these patients. Some additionally recommend the use of negative pressure rooms—however, this is not consistent across institutions. Applying a surgical face mask to those on HFNC can potentially further reduce transmission. In future pandemics, the risk of aerosolization may change based upon the characteristics of the culprit organism and therefore, recommended safety precautions must match the evidence available at that time.

23.3.3 Interhospital Transport

Patients frequently may require interhospital transportation for admission to the ICU or diagnostic/therapeutic purposes. Transport of patients who are dependent on HFNC or NIV is a particular challenge with unique considerations with COVID-19. Many conventional HFNC devices may rely on electric current without an option for battery power. However, newer transport ventilators may have the capacity to deliver high flows and oxygen for the purpose of transport. Important considerations for interhospital transport for ventilator-delivered-HFNC in general include (1) ensuring sufficient oxygen supply, (2) ensuring the sufficient battery life of the ventilator for the duration of transport. Additional considerations during the pandemic include the potential risk of aerosol dispersion with COVID-19. Many health care teams first evaluate if transportation can be successful without the need for HFNC (i.e. trial of tavish mask for a period of time before transport) [19]. Alternatively,

some institutions apply a surgical facemask to the patient during transfer with HFNC to minimize any potential risk of aerosols while the transport team wears full personal protective equipment including N-95 masks.

23.3.4 Evidence for Non-invasive Oxygenation Supports in COVID-19

Similar to non-COVID 19 respiratory failure, the optimal non-invasive oxygen modality remains in question for patients with COVID-19. A recent randomized controlled trial compared helmet NIV to HFNC across patients with COVID-19 admitted to the ICU. The study investigators evaluated if early use of helmet NIV increased the number of days free of respiratory support (defined as HFNC, NIV or invasive ventilation) at 28 days [20]. Across 110 patients (55 in each arm), the trial's respiratory support free days did not differ [20 days (interquartile range, 0–25)—helmet NIV vs 18 days (interquartile range 0–22)—HFNC; mean difference, 2 days [95% CI, −2 to 6]; $P = 0.26$]. Interestingly, the rates of endotracheal intubation and days free of invasive mechanical ventilation at 28 days were statistically in favor of helmet NIV. The rate of endotracheal intubation in the helmet NIV group was 30% compared to 51% in the HFNC group (−21% [95% CI, −38% to −3%]; $P = 0.03$). The median number of days free of invasive mechanical ventilation within 28 days in the helmet group vs. the HFNC group (28 [IQR, 13–28] vs 25 [IQR 4–28]; mean difference, 3 days [95% CI, 0–7]; $P = 0.04$). This was the first trial directly comparing helmet NIV to HFNC. It suggests that helmet NIV may protect against the need for endotracheal intubation, but further research is required to substantiate this secondary outcome.

Further support for non-invasive strategies which provide positive pressure is suggested by the RECOVERY-RS trial, which is currently in pre-print [21]. In this adaptive RCT, 1272 patients were randomized to receive HFNC, CPAP by facemask, or conventional oxygen. The primary outcome was a composite of endotracheal intubation or mortality within 30 days of enrollment. When compared to conventional oxygen, CPAP (mean of ~10 cm H_2O) significantly reduced mortality or intubation (unadjusted odds ratio 0.72; 95% CI 0.53–0.96, $P = 0.03$), while HFNC compared to oxygen therapy did not (unadjusted odds ratio 0.97; 95% CI 0.73–1.29, $P = 0.85$).

23.3.5 Patient Positioning

Prone positioning is standard of care for invasively ventilated patients with moderate to severe acute respiratory distress syndrome based on robust physiological and clinical evidence [22, 23]. There were anecdotal reports of success with awake, non-intubated, prone positioning early in the pandemic. This led to a series of randomized trials evaluating prone positioning across mildly hypoxic patients on the

wards and moderately hypoxic patients in the ICU. One clinical trial of 1126 patients requiring HFNC assessed whether prone positioning improved treatment failure as defined as intubation or mortality by 28 days [24]. The primary outcome of interest in this trial was death or intubation at 28 days. Treatment failure (mainly driven by intubation) occurred in 223 (40%) of 564 patients assigned to awake prone positioning and HFNC and 257 (46%) of 557 patients assigned to standard care with HFNC (relative risk 0.86 [95% CI 0.75−0.98]). Physiological variables (respiratory rate, ROX index, and oxygenation) all improved when moving from the supine to prone position. Importantly, the rates of adverse events were not different between the two groups. More trials are underway evaluating the criteria for consideration of prone positioning and thresholds for intubation. There are no head-to-head comparisons of prone positioning on HFNC compared to helmet NIV. However, it should be noted that 60% of the patients in the HFNC arm of the prior helmet trial underwent prone positioning compared to supine helmet NIV [20].

23.4 Conclusion

The COVID-19 pandemic has imposed unprecedented challenges on healthcare systems worldwide. Both HFNC and NIV delivered through a face mask or helmet interface have supportive physiological and clinical evidence. Care must be delivered in a way that is both efficacious to patients and prioritizes safety of the caregivers. Unique considerations surrounding location of use, aerosolization, and transport are important when adopting these devices during future pandemics.

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Invasive Ventilation in COVID-19

24

Giacomo Grasselli, Gaetano Florio,
and Emanuele Cattaneo

24.1 Introduction

Since December 2019, millions of people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 4.5 millions of deaths have been registered worldwide. Coronavirus disease 19 (COVID-19) has a wide severity range, but the most common cause of hospitalization is COVID-19 associated pneumonia with subsequent acute respiratory failure due to alveolar and endothelial cell damage, often associated with pro-thrombotic phenomena and hyperinflammation due to cytokine release.

Up to 32% of hospitalized patients with COVID-19 requires admission to Intensive Care Unit (ICU), endotracheal intubation, and mechanical ventilation (MV) [1]. At the beginning of the pandemic, worldwide ICUs were overwhelmed by patients with COVID-19 related severe acute respiratory distress syndrome (C-ARDS) requiring respiratory support and multiple healthcare systems were adapted to cope with the extraordinary number of patients and with this new respiratory pathology that nobody knew how to handle.

Setting of mechanical ventilation in patients with COVID-19 quickly became a "hot" topic, especially due to the lack of any specific therapy against SARS-CoV-2. In the first month of the pandemics, early preliminary reports described some peculiar and specific features of C-ARDS [2], suggesting the existence of two phenotypes of the disease with different respiratory mechanics characteristic and potentially requiring a different ventilatory approach. However, subsequent studies failed to confirm this view, and many experts tend to consider C-ARDS similar to "classical" ARDS [3].

G. Grasselli (✉) · G. Florio · E. Cattaneo
Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
e-mail: giacomo.grasselli@unimi.it

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The pathophysiology of hypoxemia in C-ARDS is still incompletely understood, although a combination between ventilation/perfusion mismatch, dysregulation of pulmonary perfusion and shunt represents the most likely mechanism [3]. Even though almost 2 years have passed since the beginning of the pandemic and new therapies and vaccinations have been introduced, relatively few studies have focused specifically on respiratory mechanics, pathophysiology, and mechanical ventilator settings in patients with C-ARDS [4, 5]. Furthermore, most of the available data come from small retrospective case series. Aim of the present chapter is to summarize the available evidence on relevant aspects of invasive mechanical ventilation (IMV) setting in critically ill patients with COVID-19.

24.2 Endotracheal Intubation and Timing

Most of the patients with COVID-19 who need respiratory assistance are initially handled with non-invasive supports, including high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and non-invasive ventilation (NIV) through different interfaces. The optimal timing of intubation remains a matter of intense debate. A metaanalysis of non-randomized cohort studies was inconclusive in evaluating the effect of timing intubation on mortality [6]. Similarly to what is recommended in critically ill patients with "classical" ARDS, also in patients with COVID-19 any effort should be made to timely detect failure of non-invasive support, based on rapidity of disease progression, identification of high-risk patients, worsening of patient conditions (e.g., hypoxemia and hypercapnia severity, total work of breathing, mental status), development of hemodynamic instability and/or multi organ failure.

Endotracheal intubation in patients with COVID-19 is considered as one the highest risk procedures associated with the highest risk of contagion for healthcare personnel due to the droplet dispersion. El-Boghdadly et al. reported at the beginning of the pandemic an incidence of SARS-CoV-2 infection following endotracheal intubation of 8.5% at 21 days [7], although the risk decreased in the following months. Experts recommend using personal protective equipment (e.g., N95 respirator masks, gowns, caps, and gloves), optimizing pre-oxygenation, avoiding manual mask ventilation, and performing rapid sequence intubation with video laryngoscopy.

24.3 Mechanical Ventilation Setting

The role of mechanical ventilation is to "buy time" for the lungs to heal from the disease while maintaining an adequate oxygenation and carbon dioxide removal without providing any further harm, thus minimizing Ventilator Induced Lung Injury (VILI). Since C-ARDS, like "classical" ARDS, has proved to be a very

heterogeneous disease, it is impossible to provide a "one size fits all" recipe for ventilation setting and a personalized approach based on physiological parameter and continuous monitoring is recommended.

Table 24.1 summarizes the ventilatory settings and respiratory mechanics reported in papers which specifically analyzed cohorts of mechanically ventilated patients with COVID-19. The data clearly show that COVID-19 leads to a moderate–severe form of ARDS, with a median PaO_2/FiO_2 frequently below 150 mmHg and that the ventilation strategy is not different from that recommended in "classical" ARDS. Indeed, a lung protective ventilation setting are widely adopted, with a median TV between 6 and 8 ml/kg PBW and a plateau and airway driving pressures in the safety range. Due to the severity of the disease, median PEEP levels above 10 cmH_2O has been applied; notably, this value is significantly higher than the median level of 8.4 cmH_2O observed in the LUNG SAFE study on patients with "classical" ARDS [15].

The setting of IMV in C-ARDS patients can be summarized as follows.

- Low-volume, low-pressure ventilation
- It is universally accepted that lung rest is beneficial, especially in injured lungs that are more sensible to additional harm. The seminal ARMA trial demonstrated that in ARDS a ventilation with a Tidal Volume (TV) of 6 ml/kg of predicted body weight (PBW) is associated to a better outcome compared with a TV of 12ml/kg of PBW [16]. The use of low tidal volumes (6–8 ml/kg of PBW) is recommended also in patients with C-ARDS, and it is also essential to keep airway plateau pressure and driving pressure below the protective thresholds of 30 cmH_2O and 14 cmH_2O, respectively.
- Positive end-expiratory pressure
- Positive end-expiratory pressure (PEEP) is applied to keep the lungs inflated, thus increasing end-expiratory lung volume and reducing intrapulmonary shunt. In addition, PEEP can help to minimize VILI by decreasing atelectrauma (the cyclic opening and closing of alveoli on every breath cycle) but, at the same time, an excessive PEEP level could lead to hyperinflation with possible detrimental effect both on the respiratory and cardiovascular system. In "classical" ARDS the application of high PEEP values is associated with improved outcome in patients with severe ARDS, while it does not confer any benefit in patients with mild hypoxemia [17]. As previously underlined, shunt is presumably the main mechanism of hypoxemia in C-ARDS, but also dysregulation of pulmonary perfusion, loss of hypoxic vasoconstriction, and ventilation/perfusion mismatch may play a significant role. Moreover, some patients with C-ARDS, particularly during the early phases of the disease, are severely hypoxemic despite relatively preserved values of respiratory system compliance. In this setting, the use of high PEEP is controversial. One of the most frequently adopted approaches for PEEP titration is the use of the ARDSnet table which matches a specific level of PEEP to the fraction of inspired oxygen (FiO_2) required by the patient. This

Table 24.1 Ventilatory settings and respiratory mechanics reported by most relevant studies. *PBW* predicted body weight, *RR* respiratory rate, *PEEP* positive end-expiratory pressure, *CRS* compliance of respiratory system, PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen

Study	Sample size	Tidal volume (ml/kg PBW)	RR (breaths/min)	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	Driving pressure (cmH_2O)	C_{RS} (ml/cmH_2O)	PaO_2/FiO_2 (mmHg)
Schmidt [8]	4643	6.1 [5.8–6.7]		12 [10–14]	24 [21–27]	13 [10–17]	33 [26–24]	154 [106–223]
Estenssoro [9]	1990	6.1 [6–7]	24 [20–26]	10 [8–12]	23 [20–26]	12 [10–14]	36 [29–44]	160 [111–218]
Ferrando [10]	742	6.9 [6.3–7.8]	24 [20–30]	12 [11–14]	25 [22–29]	12 [10–16]	35 [27–45]	120 [83–177]
Zanella [11]	707	7.1 [6.4–7.9]	20 [16–22]	12 [10–15]	24 [22–27]	12 [9–14]	41 [33–51]	129 [93–180]
Patel [12]	633	6.8 [6–7.8]	19 [16–22]	10 [8–12]	26 [23–29]			137 [98–189]
Botta [13]	553	6.3 [5.7–7.1]	20 [18–24]	14 [11–15]		14 [11–16]	32 [26–40]	159 [129–201]
Grasselli [1]	301	7 [6.3–7.6]	20 [18–24]	13 [10–15]	24 [22–26]	11 [9–14]	41 [33–52]	124 [89–164]
Cummings [14]	257	6.2 [5.9–7.2]		15 [12–18]	27 [23–31]	15 [11–18]	27 [22–36]	129 [80–203]

method is easy to perform and may be very useful in the context of a pandemic, where dozens of critically ill patients are admitted to ICU and physicians with low or no experience in the management of ARDS may be involved in the care of these patients. However, outside this emergency context, a personalized approach to PEEP titration should be adopted by monitoring lung recruitability (e.g., assessed CT scan, electrical impedance tomography or calculating recruitment to inflation ratio), and assessing the effect of different PEEP levels on gas exchange, respiratory mechanics, and hemodynamics.

- Spontaneous breathing
- A very interesting and challenging question in mechanically ventilated patients with C-ARDS regards the optimal timing of the switch from controlled ventilation to spontaneous assisted breathing. It is well known that maintenance of spontaneous breathing activity is associated with several advantages, such as improved ventilation-perfusion matching, prevention of muscle atrophy or weakness, reduced need for sedative drugs, and lower hemodynamic impact. On the other hand, a too early switch to spontaneous breathing in a patient with "unstable" lungs could led to dyspnea, anxiety, increased oxygen consumption and higher ventilatory requirement, ventilator asynchrony and patient self-inflicted lung injury (PSILI), eventually resulting in worsening of the patient's respiratory function. Available studies in patients with C-ARDS show that this disease requires prolonged IMV, with a median duration of MV higher than that reported in the LUNG SAFE study (10 versus 8 days) [1, 11, 15]. For these reasons, the switch to spontaneous breathing should be very careful and accomplished only when there are clear signs of lung healing such as a stable improvement in PaO_2/FiO_2, a decrease of inflammatory biomarkers and reduced ventilation requirements.

Figure 24.1 summarizes the ventilator settings and monitoring advisable in those patients.

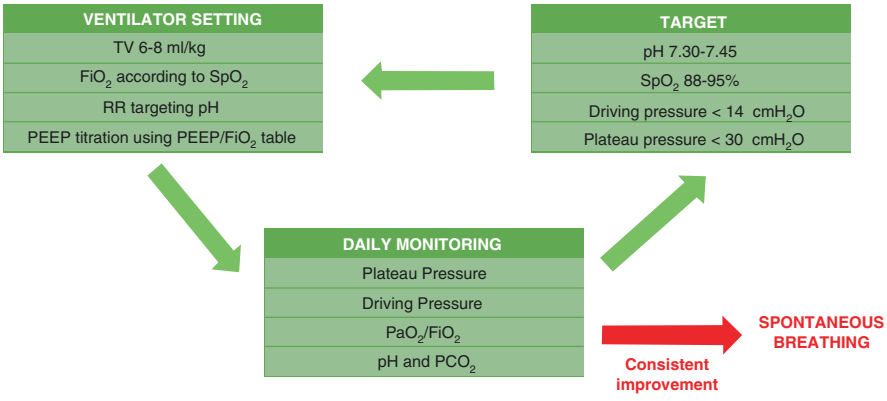

Fig. 24.1 Ventilator settings and monitoring in mechanically ventilated patients with COVID-19. *TV* tidal volume, *FiO_2* fractional inspired oxygen, *RR* respiratory rate, *PEEP* positive end-expiratory pressure, *SpO_2* peripheral oxygen saturation, *PaO_2/FiO_2* ratio of arterial oxygen partial pressure to fractional inspired oxygen

24.4 Rescue Therapies

Rescue therapies for refractory hypoxemia are widely used due to the profound hypoxemia of critically ill patients with COVID-19 and are summarized in Table 24.2. Specifically, most of the published studies reported the use of neuromuscular blockade in up to 88% of the patients [1, 8, 10] and of prone positioning in up to 77% [8, 10]. Prone positioning is usually applied when PaO_2/FiO_2 is less than 150 mmHg and it decreases atelectasis and enhances ventilation/perfusion matching, thus improving oxygenation while reducing the risk of VILI. A large randomized controlled trial in patients with early ARDS demonstrated a significant improvement in survival associated with the use of prone positioning [18]. Prone positioning is more beneficial when applied during the early stages of ARDS and if cycles of least 12–16 h/day are performed. Despite its clear efficacy in moderate–severe ARDS, in the pre-pandemic prone positioning was widely underused: in the LUNG SAFE study, it was applied only in 7.9% of the patients with ARDS [15]. At variance, recent studies show that the frequency of use of prone positioning in patients with C-ARDS is much higher, exceeding 70% in some reports. A recent study conducted in 24 Italian ICUs and involving more than 1000 patients with C-ARDS detected the use of prone positioning in 61% of them. Seventy-eight percent of patients who received prone positioning positively responded showing an increase in PaO_2/FiO_2 ratio ≥20 mmHg; furthermore, ICU mortality was lower in this subgroup compared to patients who did not respond to the rescue maneuver [19]. Mathews et al. in a recent multicentric observational study on 2338 patients mechanically ventilated patients with COVID-19 found that the risk of ICU death was lower in patients who received early prone positioning within the first 2 days of ICU admission compared who did not [20].

Table 24.2 Rescue therapies for hypoxemia in mechanically ventilated patients with COVID-19 reported by most relevant studies. *NMBA* neuromuscular blocking agents, *EXCMO* extracorporeal membrane oxygenation

Study	NMBA	Prone positioning	Pulmonary vasodilator	ECMO	Death
Schmidt [8]	1966/2224 (88%)	1556/2223 (70%)	425/2224 (19%)	235/2153 (11%)	1298/4244 (31%)
Estenssoro [9]		1176/1909 (61%)		1/1909 (<1%)	1088/1909 (57%)
Ferrando [10]	536/742 (72%)	564/735 (77%)		21/738 (2.4%)	241/742 (32%)
Zanella [11]	634/752 (84%)	471/1137 (41%)	90/1137 (8%)	30/1137 (3%)	428/1260 (34%)
Patel [12]	434/617 (70%)	273/551 (50%)	128/521 (25%)		274/633 (43%)
Botta [13]	183/487 (38%)	283/530 (53%)		2/553 (<1%)	203/530 (38%)
Cummings [14]	51/203 (25%)	35/203 (17%)	22/203 (11%)	6/203 (3%)	101/257 (39%)

Despite the available evidence on the efficacy of neuromuscular blocking agents in "classical" ARDS is controversial, these drugs are commonly employed in the most severe patients with C-ARDS, who frequently require prolonged periods of controlled ventilation. Literature data specifically focusing on the use of neuromuscular blocking drugs in mechanically ventilated patients with C-ARDS are scarce. A preliminary, retrospective report (published only as abstract) on a large cohort of patients with COVID-19 suggests that the use of neuromuscular blockers might be associated with increased 28-day mortality, prolonged mechanical ventilation and prolonged ICU stay [21]. Since the available evidence does not allow to draw any conclusion, we suggest that neuromuscular blockers should be administered to patients with refractory hypoxemia and/or ventilator asynchronies.

Inhaled pulmonary vasodilators (in particular nitric oxide) have been employed less frequently, ranging from 8% [11] to 25% [12]. These drugs may play a role in patients with severe hypoxemia, especially if coexisting with acute pulmonary hypertension and right heart dysfunction. Data to support the use of inhaled nitric oxide in mechanically ventilated patients with C-ARDS are limited and often related to specific groups of patients (e.g., spontaneous breathing subjects, pregnant women); however, a randomized control trial is ongoing to assess the clinical efficacy in mechanically ventilated patients [22].

Extracorporeal membrane oxygenation (ECMO) has been rarely used at the beginning of the pandemic, being a time- and resource consuming technique poorly compatible with the massive request for ICU admission during the first waves of the disease. In the published series, the frequency of use of ECMO in patients with C-ARDS ranges from 1% to 11%. A metanalysis of four studies from China conducted in the first month of the pandemic showed no difference in mortality when ECMO was compared with standard therapy and suggested that ECMO may not be beneficial in patients with C-ARDS [23]. However, these findings have been challenged by more recent data [24], that demonstrate that in experienced centers ECMO for C-ARDS is associated with a mortality similar to that reported in the EOLIA trial in "classical" ARDS. Recent internationals guidelines suggest that ECMO should be considered in highly selected patients who show severe refractory hypoxemia despite maximizing of all traditional therapies for ARDS including prone positioning [25].

24.5 Tracheostomy

Tracheotomy is usually performed in patients requiring prolonged invasive ventilation. There still exists a huge heterogeneity both in the technique utilized and in the timing of the procedure, with some evidence suggesting that early tracheotomy may reduce the length of mechanical ventilation and the ICU length of stay [26]. However, in the early phases of the COVID-19 pandemic most guidelines suggested late tracheotomy because of the high risk of infection for healthcare workers and because of the large use of prone positioning in the early phases of the disease [27]. A meta-analysis of 18 studies in 3234 patients showed a cumulative incidence of

late tracheotomy (14 or more days after intubation) of 71.5%, which is considerably higher than that observed in the pre-COVID-19 era [28]. However, recent data from different centers show that a tracheotomy can be performed safely, at the patient's bedside, if the recommendations on the use of personal protective equipment are rigorously followed [29]. In addition, a recent multicenter prospective trial evaluating the timing of tracheotomy in 696 critically ill mechanically ventilated COVID-19 patients showed that early tracheotomy may potentially shorten the duration of mechanical ventilation and ICU stay, without changing complications or mortality rates and therefore might be preferable, when feasible [30].

24.6 Conclusions

Current evidence shows that management of mechanical ventilation in patients with C-ARDS is similar to that recommended in "classical" ARDS. In particular, a protective strategy based on the use of low tidal volume, low plateau pressure, and low driving pressure should be implemented in all patients with C-ARDS. Individualized and personalized setting of ventilatory parameters based on bedside monitoring of respiratory mechanics, gas exchange, and hemodynamics is desirable in patients with COVID-19 related acute respiratory failure.

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Mechanical Ventilation in Different Surgical Settings

25

Luigi Zattera, Adriana Jacas, and Carlos Ferrando

25.1 Introduction

25.1.1 Postoperative Pulmonary Complications

Postoperative pulmonary complications (PPCs) are a common medical issue worldwide due to the large number of surgeries daily performed: they are as frequent as up to 5% of all surgeries and are associated with an increase of Intensive Care Unit (ICU) admission, in-hospital length of stay and mortality [1]. A great variability in incidence and related outcomes is reported, depending mainly on clinical definition, severity and type of surgery studied; to overcome these issues and better define PPCs, a consensus statement was recently published [2].

The clinical manifestation of PPCs is wide and can range from mild postoperative hypoxemia to severe respiratory failure requiring endotracheal intubation and prolonged mechanical ventilation (MV) in the ICU; as the severity varies substantially, also the etiology is broad and mainly due to atelectasis, pneumonia, aspiration pneumonitis, and adult respiratory distress syndrome (ARDS). Other respiratory manifestations such as pleural effusion, pneumothorax, bronchospasm are also described, although they don't share the same biological mechanism [2].

As discussed above, frequency of PPCs is not uniform among patients: multiples risk factors showed to be associated with PPCs, both patient- and procedure-related, which are resumed in Table 25.1; several scores were developed for this purpose: the ARISCAT score [1] predicts PPCs based on the preoperative conditions of the patient and the characteristics of the surgery, while the SLIP score is more focused on the risk of postoperative lung injury and (ARDS) [3]. Finally, the LAS VEGAS

L. Zattera (✉) · A. Jacas · C. Ferrando
Department of Anesthesia and Intensive Care, Hospital Clínic, Barcelona, Spain
e-mail: LZATTERA@clinic.cat

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Table 25.1 Summary of the most common risk factors for postoperative pulmonary complications. *ASA* American Society of Anesthesiology Physical Status Classification System, *COPD* chronic obstructive pulmonary disease, *CHF* chronic heart failure, *OSA* obstructive sleep apnea, SpO_2 peripheral hemoglobin oxygen saturation

Patient-related	Procedure-related
Age	Upper abdominal surgery
Male sex	Thoracic surgery
ASA ≥ II	Head and neck surgery
Frailty/functional dependence	Major vascular surgery
Impaired sensorium	Emergency surgery
Smoking	Surgery lasting more than 2 h
COPD/Asthma	Perioperative nasogastric tube
CHF	Residual neuromuscular block
OSA	Mechanical ventilation strategy
Obesity	Intraoperative low SpO_2
Alcohol abuse	Intraoperative use of vasopressors
Chronic liver disease	
Active cancer	
Preoperative anemia	
Low preoperative SpO_2	

risk score includes both ARISCAT cohort risk factors together with intraoperative variables [4].

Moreover, the Air-Test in the postoperative period is a validated score that assesses the basal peripheral oxygenation before and 3 h after admission to the postoperative care unit and is a useful tool to screen at risk patients for PPCs both intraoperatively and in the early postoperative period [5].

Once patients at risk are detected, several interventions can be made with the aim of reducing PPCs, like preoperative patient optimization with prehabilitation, titration of previous medical treatment, administration of an adequate postoperative analgesia and physiotherapy. Finally, a protective MV strategy must be considered to minimize its negative effects on lung function.

25.1.2 Protective Mechanical Ventilation: Basic Concepts

It has been described that the vast majority of patient undergoing general anesthesia will develop atelectasis to a certain degree: the cephalad shift of the diaphragm causes basal lung collapse, which is generally worsened by the inflation of pneumoperitoneum or if the patient is obese. The MV in this scenario must minimize the damage caused by positive pressure ventilation, such as tidal overdistension (i.e. volutrauma) and alveolar cyclic end-expiratory collapse/recruitment (i.e. atelectrauma), especially present in areas where lung is collapsed. Volutrauma is reduced by setting of a low-tidal volume (V_T) of 6–8 ml/kg of Ideal Body Weight (IBW) while atelectrauma by the application of a positive end-expiratory pressure (PEEP)

that prevents end-expiratory lung collapse. In addition, the atelectasis induced by general anesthesia will increase the Driving Pressure (DP), a surrogate of lung strain.

In other words, a low V_T and the application of certain degree of PEEP is nowadays the standard of practice: however, although a V_T of 6 ml/kg IBW accompanied with the application of variable amounts of PEEP showed generally to reduce PPCs if compared to a far non-protective strategy [6], larges RCTs failed to show a PPCs benefit when an arbitrary PEEP was applied to a heterogeneous population in terms of the patients' risk factors and surgical techniques [7], remarking the concept that maybe "one size doesn't fit all": in high risk patients and during certain procedures such as in one-lung ventilation (OLV) or laparoscopic surgery, patients do not benefit from a "low V_T only" strategy, and other factors must be taken in account, making protective MV a more patient-targeted concept.

25.1.3 Personalized PEEP: The Open Lung Approach (OLA)

The Open Lung Approach (OLA) is an emerging ventilatory strategy that aims to titrate PEEP according to individual characteristics. It consists in performing a recruitment maneuver (RM) to open the collapsed alveoli and to set a PEEP that minimizes the cyclic lung collapse and maintain the lung open in a safety range. Several randomized clinical trials (RCT) studied the possible benefits of OLA in different surgical settings (Table 25.2): although it is clear that protective MV based on PEEP application and low V_T is better than a zero-PEEP and high V_T approach, studies comparing OLA with the conventional protective MV generally failed to improve the outcomes in terms of PPCs, at least in unselected populations. However, OLA seems to bring benefits on gas exchange and the respiratory mechanics as discussed later on.

Before adopting an OLA strategy, several considerations must be made:

- Identify the patients at risk: aside of the previously mentioned risk scores which can be used to screen patients preoperatively, the intraoperative Air-Test, is a novel and validated method that consists in the reduction of the FiO_2 to room air after anesthesia induction and in a subsequent check of the peripheral oxygen saturation: if lower that 97%, a shunt due to atelectasis is present and the patient could benefit of an OLA [13].
- Type of surgery: the OLA could benefit especially bariatric surgeries, OLV, laparoscopic surgeries, and Trendelemburg position.
- When to perform a RM: usually at the beginning of the surgical procedure and at the end before emerge and extubation, in a time interval approach during the whole procedure or by monitoring more clinical triggers such as hypoxemia, low peripheral blood oxygen saturation or a worsening in respiratory mechanics.
- Type of RM performed: a RM, in order ro recruit collapsed lung areas, has the aim to reach the alveolar opening pressure, which is usually 40 cmH_2O; RM's were classically performed via the application of a continuous positive airway

Table 25.2 Recent RCTs comparing different protective ventilation strategies. V_T tidal volume, *IBW* ideal body weight, *RM* recruitment maneuver, *PEEP* positive end-expiratory pressure, *OLA* open lung approach, *PPCs* postoperative pulmonary complications

Author (reference)	Type of surgery	Control group	Interventional group	Outcomes
Severgnini et al. [34]	Open abdominal surgery	*N* = 27 V_T = 9 ml/kg IBW No RM PEEP = 0 cmH_2O	*N* = 27 V_T = 7 ml/kg IBW Stepwise RM PEEP = 10 cmH_2O	Low V_T and PEEP reduced PPC incidence
Futier et al. [6]	Abdominal surgery	*N* = 200 V_T = 11 ml/kg IBW No RM PEEP = 0 cmH_2O	*N* = 200 V_T = 6–8 ml/kg IBW RM = 30–30–30 PEEP = 6 cmH_2O	Low V_T and PEEP reduced PPC incidence
Costa Leme et al. [8]	Cardiac surgery (postoperative)	*N* = 163 V_TVT= 6 ml/kg IBW RM = 20–30–3 times PEEP = 8 cmH_2O	*N* = 159 V_TVT= 6 ml/kg IBW RM= 45–60–3 times PEEP= 13 cmH_2O	OLA reduced PPC
Ferrando et al. [9]	Abdominal surgery	*N* = 499 V_TVT = 8 ml/kg IBW No RM PEEP = 5 cmH_2O	*N* = 513 V_TVT = 8 ml/kg IBW Stepwise RM PEEP to best Crs	OLA reduced PPC *Secondary outcome*
Park et al. [10]	Thoracic surgery	*N* = 147 V_TVT = 6 ml/kg IBW No RM PEEP = 5 cmH_2O	*N* = 145 V_TVT = 6 ml/kg IBW No RM PEEP to lowest DP	OLA reduced PPC
Bluth et al. [11]	Obese patient	*N* = 987 V_TVT = 7 ml/kg IBW RM PEEP = 12 cmH_2O	*N* = 989 V_TVT = 7 ml/kg IBW No RM PEEP= 5cmH_2O	No differences
Lagier et al. [12]	Cardiac surgery	*N* = 247 V_TVT = 6–8 ml/kg IBW No RM PEEP = 2 cmH_2O	*N* = 246 V_TVT = 6–8 ml/kg IBW RM: repetitive 30–30 PEEP = 8 cmH_2O	No differences
Karalapillai et al. [7]	All surgeries	*N* = 592 V_TVT = 10 ml/kg IBW No RM PEEP = 5 cmH_2O	*N* = 614 V_TVT = 6 ml/kg IBW No RM PEEP = 5 cmH_2O	No differences

pressure (CPAP) of 30–40 cmH_2O for a variable amount of time: this approach has several limitations and nowadays it is not recommended firstly because of an higher impact on patient's hemodynamics and secondly because this method does not allow a personalized PEEP setting; to achieve the latter, a stepwise approach with initial recruitment and a personalized PEEP fixed by an mechanical variable are more reliable, as showed in Fig. 25.1: PEEP can be titrated by optimizing Plateau Pressure (Pplat), DP, respiratory system compliance (Crs), oxygen saturation at room air [13] or can be guided by novel non-invasive monitoring techniques such as electrical impedance tomography, indirect measurement of transpulmonary pressure (TP) through an esophageal probe or evaluating the aeration pattern with LUS.

- Contraindications for RM, which are seldom absolute:
  - Patients with COPD or asthma, especially if *bullae* or previous pneumothorax are present.
  - Hemodynamic instability: although a stepwise RM produces less impact on the patient's hemodynamics, the TP increase may cause transitory hypotension especially in hypovolemic patients and in patients with acute cor

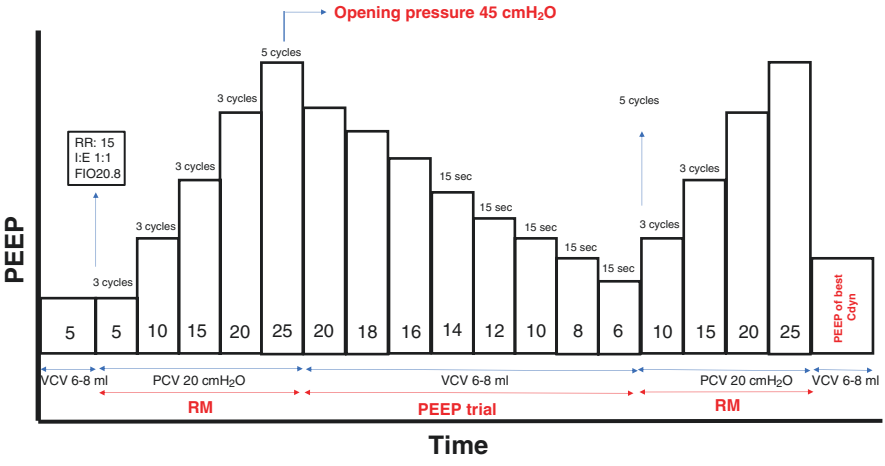

Fig. 25.1 Stepwise approach to perform a recruitment maneuver: after switching to a pressure-controlled mode, a PEEP level of 5 cmH_2O is increased in 5 cmH_2O steps each lasting three breaths maintaining a fixed DP of 20 cmH_2O until a recruitment inspiratory pressure of 45 cmH_2O is reached which is then maintained for five breaths. In the following decremental PEEP titration trial, the ventilation mode is switched back to volume control with the same settings used during baseline but an initial PEEP of 20 cmH_2O which was then reduced in steps of 2 cmH_2O each maintained for 15 s. The optimal PEEP is identified as the value corresponding to the highest Cdyn found during the decremental PEEP titration trial. Finally, a new RM is performed to re-open collapsed alveoli and the optimal PEEP is applied and maintained during the rest of the surgery or until a worsening in respiratory mechanics or oxygenation is detected. *VCV* volume-control ventilation, *PCV* pressure-control ventilation, *RR* respiratory rate, *I:E* inspiratory to expiratory time ratio, FiO_2 inspired oxygen fraction, *RM* recruitment maneuver, *PEEP* positive end-expiratory pressure, *Cdyn* dynamic compliance

pulmonale. In these patients, previous resuscitation with fluids and vasopressors must be considered.
– Patients with acute cerebral injury at high risk to develop intracranial hypertension, that will be considered later in this chapter.
– Open ophthalmic surgery.

25.2 Laparoscopic Surgery

Laparoscopic surgery (LPS) is gaining popularity worldwide due to its minimal invasiveness. However, the inflation of CO_2 in the peritoneum causes an increase in intra-abdominal pressure (IAP) with subsequent cephalad shift of the diaphragm, increasing the pleural pressure and creating negative P_L, and eventually worsening the anesthesia-induced atelectasis and shunt [14]. This is worsened by the frequent use of Trendelenburg position.

As a direct consequence, a protective low V_T could not be sufficient to maintain a positive P_L and consequently the lung will further collapse.

25.2.1 Current Evidence

In a large recent RCT, an OLA approach plus postoperative CPAP showed a PPCs benefit (although as a secondary outcome) when compared to protective ventilation of Vt 8 ml/kg of IBW and a PEEP of 5 cmH_2O in a mixed of LPS (40% total) and open abdominal surgery, possibly infra-estimating the effect on LPS population [9]. In another observational study, a PEEP of 5 cmH_2O was able to reverse the shunt effect in open surgery while only a PEEP of 10 cmH_2O was able to ameliorate shunt on LPS [15].

25.3 Obese Patients

In obese patients, the cephalic shift of the diaphragm leads to a further reduced functional residual capacity (FRC) after general anesthesia compared to normoweighted patients, making obese patients even more prone to atelectasis in both open and LPS. Furthermore, in obese patients, lung compliance could be further reduced in the presence of chronic heart disease and due to increased chest wall elastance. Finally, an expiratory flow limitation usually exists, especially in lying position or in Trendelenburg position. The result is that obese patients during general anesthesia are both prone to atelectasis and shunt as well as auto-PEEP development, making obesity a condition prone to PPCs per se in all types of surgery.

The increasing use of laparoscopic surgical techniques in both bariatric and non-bariatric abdominal surgery makes PEEP titration especially challenging for this category of patients: due to the increased chest wall elastance, in obese patients

there is an increased difference between DP and P_L making Crs, Pplat, and DP less useful in monitoring the respiratory mechanics. Several emerging techniques, such as direct measuring of P_L, LUS, and electrical impedance tomography, seem promising in obese patients.

25.3.1 Current Evidence

In obese patients an approach of RM and an arbitrarily high PEEP does not seem sufficient as demonstrated in the recent PROBESE trial, a large RCT where an approach based on RM plus a relatively high PEEP of 12 cmH_2O failed to demonstrate better outcomes in terms of PPCs after non-cardiac and non-neurological surgery when compared to a standard PEEP of 5 cmH_2O [11].

Again, a fixed high PEEP after a RM does not seem the right approach: in two recent pilot studies, the use of OLA and a personalized PEEP showed better oxygenation and respiratory mechanics than PEEP alone: in a single-center study a RM plus a PEEP titration according to best regional ventilation distribution measured with electrical impedance tomography showed better oxygenation and a more homogeneous distribution of the tidal volume [16] in the intervention group. Interestingly, the same group showed similar results when comparing the individualized PEEP with both the low PEEP and the RM plus fixed PEEP of 12 cmH_2O, showing that the individualized PEEP, with a median PEEP of 18 cmH_2O (therefore far higher than 12 cmH_2O) was associated with better respiratory mechanics and gas exchange [17].

Another physiological study with multimodal non-invasive monitoring such as pulse oximetry, volumetric capnometry, esophageal pressure, and Crs showed better respiratory mechanics if a personalized PEEP after a RM was set in comparison to a relatively high PEEP of 8 cmH_2O [18]. Finally, a LUS-based approach of PEEP titration is a promising technique that can further help to monitor MV in obese patients [19].

25.4 Thoracic Surgery

During thoracic surgery, OLV is usually performed in lateral decubitus to facilitate surgical access: in this situation the upper lung (i.e. nondependent lung) is collapsed while the dependent lung is ventilated.

Patients receiving OLV are at especial risk of hypoxemia and PPCs due to several factors: first, because of the presence of a degree of shunt due to residual perfusion of the nondependent lung besides pulmonary hypoxic vasoconstriction reflexes; this phenomenon might vary depending on comorbidities and of the choice of anesthetic drugs; third, the presence of atelectasis in the dependent lung due to general anesthesia and due to a decreased chest wall compliance caused by the direct contact of the ribs with the operating table; fourth, a protective ventilation with low V_T must be tailored to the dependent lung, with further reduction of V_T and an increased risk of

atelectasis. Finally, patient's comorbidities, which are often the *primum movens* for the surgical indication (i.e. COPD, lung cancer…), that usually consists in some degree of lung resection, make them prone to develop PPCs, as described in a post-hoc analysis of the LAS VEGAS study, where PPC in moderate-to-high risk patients reached an incidence as high as 48,1%, with an increase of hospital length of stay [20].

25.4.1 Current Evidence

In a recent, large retrospective study, a V_T of 5 ml/kg/IBW and a PEEP od 5 cmH_2O failed to demonstrate a reduction in PPCs [21], although a clinical trial showed that low V_T and a 5-to-8 PEEP application compared to high V_T and zero-PEEP showed better outcomes in OLV, in terms of major PPCs and hospital length of stay [22]. These results highlight that in OLV the main determinant of protective ventilation is the set of PEEP. The main question about how to set the PEEP remains uncertain, although a "lowest DP" approach seems reasonable: Park et al. randomized 292 patients to either conventional protective ventilation (6 ml/kg/IBW, PEEP of 5 cmH_2O and RM) or conventional protective ventilation plus a PEEP titration to the lowest DP during OLV, showing less PPCs in the postoperative period [10].

25.5 Cardiac Surgery

A positive pressure ventilation increases the mean intrathoracic pressure causing several effects in the cardiac hemodynamics which are resumed in Fig. 25.2. The right ventricular cardiac output is reduced by two mechanisms: a decrease in pre-load secondary to an increased right atrial pressure and an increase in afterload by an overdistension of peri-alveolar vessels and collapse of intra-alveolar vessel in collapsed dependent areas. Left ventricular preload is initially increased by alveolar vessel squeezing, but finally is reduced due to lowered right cardiac output; finally, left ventricular performance is normally increased due to a reduction of its transmural pressure and afterload. The net effect of this interaction is a decreased cardiac output mainly due to a decreased right cardiac output.

25.5.1 Current Evidence

The OLA strategy is not very common in cardiac surgery: first, a RM in a right ventricle with poor functional reserve could further worsen the right cardiac output; moreover, a cardiac surgery includes three different phases: anesthesia induction, the on-pump operative time and the pump-exit, and anesthesia emerge. This complicates the interpretation of studies since different stages could benefit from different ventilatory strategies.

As showed in a small trial, after a transitory hemodynamic worsening OLA could improve the effects on right cardiac hemodynamics and gas exchange by

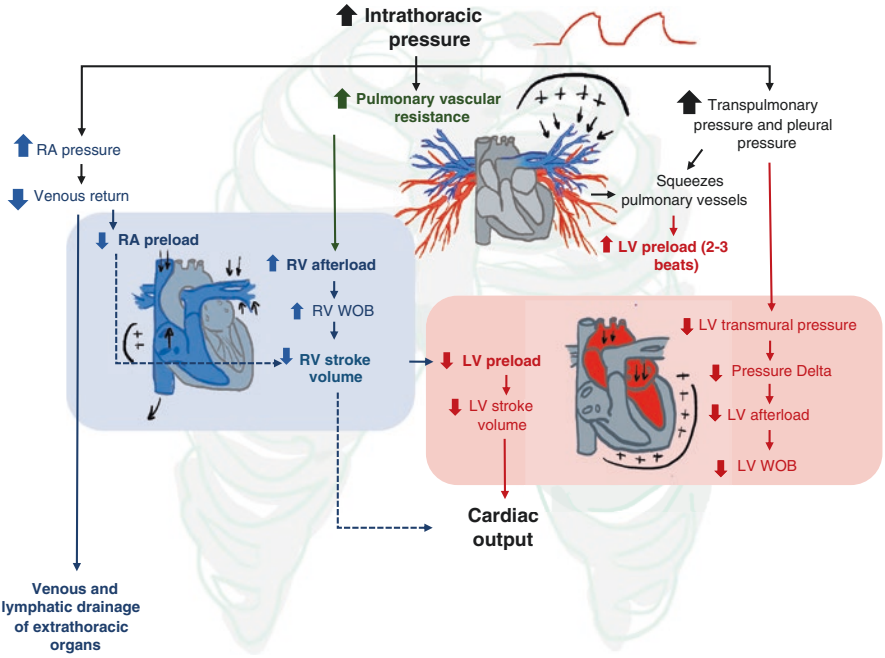

Fig. 25.2 Heart–lung interactions during positive pressure mechanical ventilation. *RA* right atrial, *HVC* hypoxic vasoconstriction, *RV* right ventricular, *LV* left ventricular, *SV* stroke volume

opening collapsed vessels present in atelectasis, improving oxygenation and consequently reducing the hypoxic vasoconstriction [23].

During on-pump ventilation, a low-tidal low-PEEP strategy seems to successfully reduce PPCs, with high DP being the variable most associated with worse outcomes [24], while MV with OLA does not seem to reduce PPCs, as showed in a large RCT of almost 500 patients with low levels of PEEP [12].

However, once the on-pump phase is finished, the OLA approach could lead to better outcomes: as showed in a small RCT, a ventilatory strategy including a RM followed by PEEP 10 cmH_2O after the end of surgery, showed better right ventricular performance and reduction in atelectasis compared with 6 cmH_2O PEEP [25], although patients' population had relatively good cardiac baseline characteristics.

Finally, during the postoperative period, an intensive OLA approach seems to reduce PPCs in patients with postoperative hypoxemia [8].

25.6 Neurosurgery

The effects of MV on brain homeostasis are the result of a complex interaction between cerebral circulation, the characteristics of the patient, and type of surgery: cerebral perfusion pressure (CPP) is the result of the difference between mean

arterial pressure and intracranial pressure (ICP); the former, according to the Monro-Kellie theory, is the sum of cerebral blood flow (CBF), brain parenchyma and cerebrospinal fluid (CSF). During MV, changes in ICP are mainly due to the variation in CBF as follows:

- $PaCO_2$ levels inversely change CBF: if the patient becomes hypercapnic, a vasodilatory input will be delivered to cerebral vessels, while in case of hypocapnia there will be cerebral vasoconstriction, making a direct CO_2 monitoring such as End-tidal CO_2 a cornerstone of the ventilatory management of such patients.
- Hypoxemia and respiratory failure are also strong triggers for cerebral vasodilation, especially when the PaO_2 is below 60 mmHg.
- An increased PEEP may worsen the venous return through the jugular veins, potentially causing cerebral venous congestion, especially in patients in supine position without head-tilt.

25.6.1 Current Evidence

It is a common clinical opinion that a low V_T and high PEEP could be associated both with higher $PaCO_2$ and higher ICP and that a RM could worsen CPP by reducing the CBF, making the OLA approach a rarely-used strategy in this subtype of patients [26], although in neurocritical patients a higher PEEP does not seem to affect CPP if fixed as high as 15 cmH_2O [27]. On the other hand, in neurosurgical patients, oxygenation and PaO_2/FiO_2 ratio were strong predictors of worse prognosis and death [28].

Moreover, despite a RM by continuous CPAP at 35 cmH_2O significantly increases subdural pressure and decreases CPP [29], a study by Nemer et al. [30] showed that a stepwise RM lowered CPP in a safe and reversible way compared to the classical CPAP RM, besides improving oxygenation in patients with subarachnoid hemorrhage, in alignment with the results of OLA in patients with traumatic brain injury and ARDS [31].

Finally, when compared with a conventional protective MV, it seems that a low V_T of 6 ml/kg IBW plus RM every 30 min could reduce postoperative delirium (and lower the levels of glial fibrillary acidic protein, an emerging biomarker of brain injury in elderly patients undergoing spinal surgery) [32].

25.7 Conclusions

Due to the high incidence of PPCs after surgery, a standard protective mechanical ventilation strategy must be generally considered during anesthesia. Despite the actual lack of evidence in terms of more clinically relevant outcomes such as PPCs and mortality, in certain patient populations or surgical techniques OLA shows to be

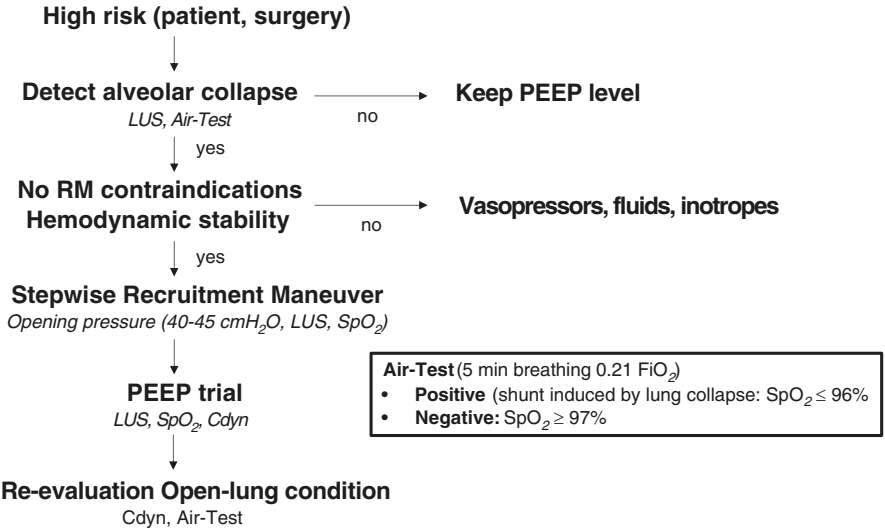

Fig. 25.3 Ventilatory strategy proposal based on OLA. *LUS* lung ultrasound, *PEEP* positive end-expiratory pressure, *Cdyn* dynamic compliance

a safe and feasible strategy that improves both oxygenation and respiratory mechanics intraoperatively.

Finally, based on the results of a post-hoc analysis [33], it seems that an open lung condition and not the OLA per se is the main factor associated to a reduced risk of developing PPCs; therefore, a reasonable ventilatory approach in the OR is proposed in Fig. 25.3: after anesthesia induction, alveolar collapse can be detected through an Air-test, a LUS examination or a worsening respiratory mechanics (i.e., Crs, DP). Once contraindications for a RM and hemodynamic stability is achieved, a RM to reach the alveolar opening pressure, followed by a decremental PEEP trial to find the optimal PEEP. Finally, respiratory monitoring will allow the clinician to detect a new alveolar collapse and perform a new RM.

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Following Up the Patients at Long Term

26

Nicola Latronico, Simone Piva, and Frank Rasulo

26.1 Introduction

Caring for critically ill patients involves a comprehensive approach to multiple organ functions with integration of complex information and rapid action. Knowledge of physiology and biochemistry, passion for clinical medicine, advanced skill to perform invasive life-supporting maneuvers and sophisticated monitoring, as well as dedication, enthusiasm, empathy, and compassion to establish exemplary patient relationships are keys to excellence in critical care medicine [1]. With continuous investments in training and improved technology, critical care has achieved, over the last 50 years, a substantial reduction in short-term mortality in several diseases. However, with decreasing mortality, the critical care community has started to learn about "the legacy" of critical illness and of the invasive treatments used to support organ function. Many intensive care unit (ICU) survivors may experience long-lasting health problems collectively named as post-intensive care syndrome (PICS) and defined as new or worsening physical, mental, and cognitive

N. Latronico (✉) · F. Rasulo
Department of Anesthesia, Intensive Care and Emergency, Spedali Civili University Hospital, Brescia, Italy

Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

"Alessandra Bono" Interdepartmental Research Center for LOng-Term Outcome (LOTO) in Survivors of Critical Illness, University of Brescia, Brescia, Italy
e-mail: nicola.latronico@unibs.it

S. Piva
Department of Anesthesia, Intensive Care and Emergency, Spedali Civili University Hospital, Brescia, Italy

Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

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impairments that arise after critical illness and persist beyond acute care hospitalization [2]. Pain, muscle weakness, dyspnea, symptoms of depression, anxiety and post-traumatic stress, and problems with attention and memory are commonly reported for months to years after surviving the acute disease [1]. Symptoms of PICS significantly impact on survivors' health-related quality of life (HRQoL) and their ability to cope with activities of daily living (ADL) and return to work, and are associated with increased use of healthcare resources and costs [3, 4]. As a matter of facts, the ICU community is realizing that we need to move beyond acute care aimed at reducing short-term mortality, to reduce long-lasting disability and improve the quality of life of ICU survivors and their families [5].

In this chapter, we propose a model to follow-up patients surviving an acute illness with a comprehensive clinical approach and describe our long-lasting experience with a follow-up clinic. We also review the most relevant clinical characteristics of PICS, the risk factors for post-ICU impairments and the strategies for their timely detection.

26.1.1 A Logistic and Cultural Framework to Assist ICU Survivors

Most studies on the long-term consequences of critical illness have been done in ARDS survivors. As a prototype of an acute disease with altered inflammatory response and multiple organ dysfunctions, ARDS represents a high-risk condition for developing long-lasting deficits after the resolution of the primary condition. We have proposed that the "A" of ARDS should also indicate "after," to emphasize "the need to address early survivorship care aimed at preventing disability after ICU with the same priority given to the treatment of the acute lung injury to reduce mortality" [6]. However, ARDS survivors do not demonstrate a specific pattern of impairments compared with other critical illnesses [7]. Moreover, sepsis [8], ICU-acquired weakness [9], and other complications arising during the ICU stay, particularly in patients with prolonged critical illness (i.e. ICU stay longer than 10 days), are themselves responsible for long-term impairments and are common to many critical care conditions. Therefore, we prefer to describe PICS as a major health problem for the global community of ICU survivors rather than a specific category of critically ill patients.

26.2 The Follow-Up Clinic and the PICS Framework

Symptoms of PICs are usually described as clustering into physical, cognitive, and mental health domains (Table 26.1). However, with progressing research new conditions have been described in ICU survivors and have been suggested as additional components of PICS, such as swallowing disorders with risk of inhalation pneumonia and malnutrition, altered bone metabolism with increased risk of fragility fracture, endocrine and metabolic disorders (including new-onset diabetes and transient alteration of cortisol and anterior pituitary hormones), sexual dysfunctions, and

Table 26.1 Health domains of the post-intensive care syndrome (PICS), measured outcomes and instruments

Domains of PICS	Measured outcome	Instruments
Physical domain		
• Body level	Muscle weakness Critical illness neuromyopathy Fatigue	MRC scale, handgrip dynamometry EMG FSS, FACIT-F
• Activities	Performance-based activity limitations Self-reported activity limitations	6-minute walk test, timed up-and-go SF-36 physical functioning
• Participation in a social context	Participation restrictions	ADL, IADL, return to work, SF-36 role physical
Cognitive domain		
	Subjectively-reported cognitive impairment Objectively-reported cognitive impairment: screening tests Objectively-reported cognitive impairment: batteries of cognitive tests	Cognitive outcomes reported by patients or their caregivers MoCA RBANS
Mental health domain		
	Depression	HADS-depression
	Anxiety disorders	HADS-anxiety
	PTSD	PTSD checklist for DSM-5, IES

The list of instruments reports some examples, it is not intended to provide a comprehensive list of available tests. More information is available with [10] (see the body text)
MRC medical research council, *EMG* electromyography, *FSS* fatigue severity score, *FACIT-F* functional assessment of chronic illness therapy-fatigue scale, *SF-36* 36-item short-form health survey, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *MoCA* montreal cognitive assessment, *RBANS* repeatable battery for the assessment of neuropsychological status, *HADS* hospital anxiety and depression scale, *PTDS* posttraumatic stress disorder checklist for diagnostic and statistical manual of mental disorders-5 (DSM-5), *IES* impact of event scale

sleep disorders [11]. Moreover, co-occurrence is common (i.e., symptoms in two or more domains) [12], and hence, the approach to post-ICU patients in clinical practice is necessarily multi-dimensional and multi-professional (Fig. 26.1) [13]. In the UK, where post-ICU assessment is recommended for all adults who stay in ICU for more than 4 days and are at risk of morbidity [14], a survey in 2006 showed that a follow-up clinic was available in 30% of 266 ICUs, and 55% of the clinics were nurse-led [15]. Only 59% of the follow-up clinics were funded, predominantly from the ICU budget.

Our follow-up clinic at Spedali Civili Hospital of Brescia, a large university-affiliated hospital serving an area of 1.2 million people in northern Italy, was founded in 2012 and has progressively increased its activity to every weekday for a total of 30 h/week. Initially, in-person assessments were performed at 6 and 12 months, but we added a 3-month visit to take care of COVID-19 patients at an

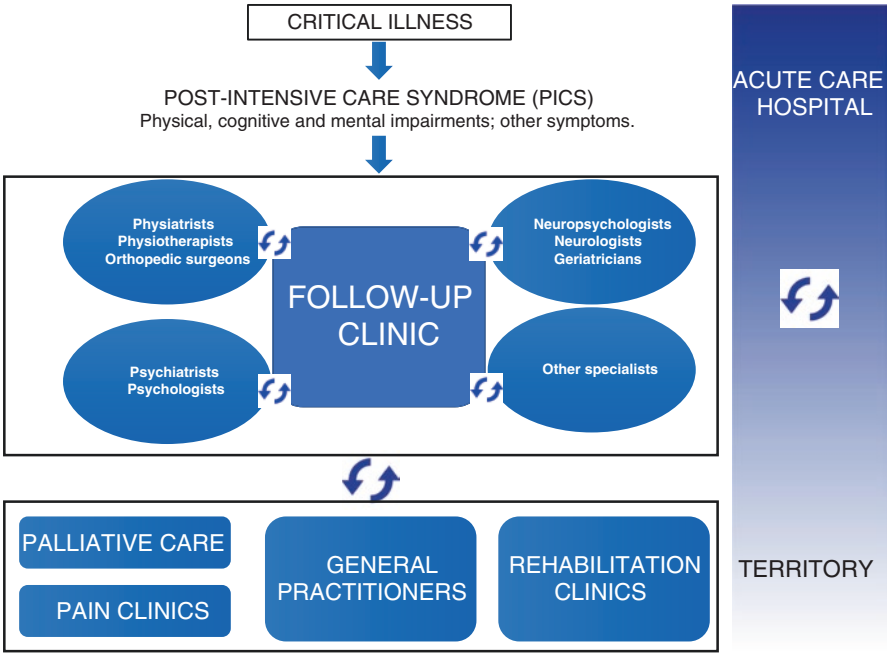

Fig. 26.1 Interactions of the Follow-Up Clinic with health care specialists and structures inside and outside the acute care hospital

earlier stage and, more recently, a 24 month visit to extend the observation period for assessing the efficacy of therapeutic interventions on long-lasting symptoms. The team consists of intensive care physicians and nurses who have been trained in the use of instruments to assess the PICS symptoms, in addition to measures of ADL and HRQoL (Table 26.1). The follow-up clinic provides direct clinical support to patients, manages referral to other specialists, and serves as a platform for research on the natural history of PICS and therapeutic interventions.

26.2.1 Physical Impairment

Normal physical functioning requires the interactions between factors at the level of the body function and structure, the whole person (activities), and the environment (the whole person in a social context) (Table 26.1). Disability involves the dysfunction of one or more of these levels. Critical illness myopathy and neuropathy is an example of structural impairment at the body level, representing the dysfunction of peripheral nerves and muscles leading to muscle weakness and persistent physical dysfunction [16]. Reduced performance at the 6-min walk test is an example of dysfunction at the level of the whole person, since the test evaluates the integrated responses of all the systems involved during walking, including the neuromuscular units, muscle metabolism, pulmonary and cardiovascular systems, blood, but also

the joints (range of motion), the brain (proprioception, balance, cognition), and the mind (motivation).

Altered physical functioning is common in ICU survivors, affecting a variable proportion of patients ranging from 20% to 80%. This variability may be due to differences in the patient populations, the specific physical domain assessed, the instruments and cutoff thresholds used, and timing of follow-up evaluation [4, 7, 13]. Physical impairments may persist for several years after ICU discharge and some patients may never recover to their pre-ICU condition [17]. A new or worsened physical problem is described in almost 40% of the medical and urgent surgical ICU patients at 1 year after ICU discharge [4]. Fatigue, a self-reported outcome with a severe impact on quality of life, is reported by 70% of ARDS survivors up 1 year [18]. At 5 years, the median distance walked in 6 minutes in ARDS survivors is 76% of the distance in an age and sex-matched control population [17]. Older patients with sepsis have a substantially increased risk of developing new functional limitations—a mean 1.6 new limitations in those with no limitations at baseline—in the years following their sepsis hospitalization compared to before sepsis hospitalization [8].

Loss of muscle mass can be profound during the acute stage of critical illness, in the order of 15–20% of the total muscle mass. Younger patients and those with greater muscle mass reserve will have a better outcome but some patients, particularly older, fragile patients with comorbidities or those with high acute disease severity, may never recover to pre-ICU state. ICU-acquired muscle weakness is a risk factor for long-term physical impairments and increased mortality [19], especially when caused by critical illness polyneuropathy or polyneuromyopathy [16]. Muscle atrophy caused by immobility has a better prognosis, but chronic muscle atrophy has been described in patients with altered muscle regrowth, possibly associated with the loss of satellite cells, the muscle stem cells responsible for muscle regeneration [20].

26.2.2 Cognitive Impairment

Cognitive impairment is an important health problem in ICU survivors and affects a variety of cognitive domains, including mental processing speed, memory, attention, and executive functions. Deficits can be protracted, with global cognition scores still reduced 1 year after hospital discharge and comparable to those commonly described in patients sustaining moderate traumatic brain injury or developing mild Alzheimer's disease [21]. Deficits are not limited to older patients or to patients with pre-existing cognitive impairments and are indeed described in people of all ages [21].

Estimates of occurrence rate are imprecise, with 6%, 11%, and 13% of elective surgery, medical and urgent surgical patients showing generalized cognitive decline at 1 year. Reported occurrence rates of cognitive impairment are much higher, 30–46%, in ARDS survivors. Occurrence rates in ARDS survivors range from 46% to 80% at 1 year, 20% to 47% at 2 years, and 20% at 5 years [17]. This variability

can be attributed to the different patients' population studied and timing of assessment; however, the type of cognitive instruments, including subjective or objective assessments, screening tests or comprehensive batteries of neuropsychological tests, largely influences detection of cognitive impairments. For example, at 3 months, the frequency of subjective cognitive impairment, as reported by patients or their caregivers, is 35% (95% CI 29–41%) and that of objective cognitive impairment, as determined using various batteries of neuropsychological tests, is 54% (95% CI 51–57%) [10]. The prevalence of cognitive impairment detected with the Mini Mental State Examination (MMSE), a screening test, is lower than that detected with neuropsychological test batteries. Indeed, MMSE has very low sensitivity in detecting cognitive impairment in ICU survivors, with the degree of cognitive impairment classified as mild in the early course of recovery and no cognitive impairment 12 months. As such, MMSE is not recommended as a screening test, as opposed to the Montreal Cognitive Assessment test, which can be used [22]. A more general discussion of cognitive screening tests, comprehensive neuropsychological test batteries and subjective cognitive decline is published elsewhere [23]. Delirium, benzodiazepines, sepsis, hypoxia, ARDS, and shock are key risk factors for post-ICU cognitive impairment [22]. First community-acquired sepsis events are associated with an almost seven-fold accelerated rate of cognitive decline compared with pre-sepsis trajectories [24]. Severe sepsis in hospitalized older people is independently associated with a tripling in the odds of moderate to severe cognitive impairment in the years after sepsis hospitalization [8]. A longer duration of delirium is independently associated with worse global cognition at the 3- and 12-month follow-up. Daily monitoring and appropriate prevention and treatment of delirium, minimization of sedation, and timely treatment of sepsis are of utmost importance to reduce not only short-term mortality but also the burden of long-term cognitive impairment.

26.2.3 Mental Health Impairment

ICU survivors have a substantial burden of psychopathology, including symptoms of depression, severe general anxiety, and post-traumatic stress disorders (PTSD) which are of common occurrence in ICU survivors and tend to co-occur across two or all three psychiatric domains in most patients [25].

Prevalence of clinically important depressive symptoms in meta-analysis is 29% at 2–3 months (95% CI 22–36%), 34% (24–43%) at 6 months, and 29% (23–34%) at 12–14 months, with symptoms persisting over the first 12 months after ICU discharge [26]. In a large multicenter postal survey of self-reported depression in the UK, patients with symptoms of depression were 47% more likely to die during the first 2 years after discharge from ICU than those without [25]. Pre-existing depression and psychological distress are strongly associated with a greater risk for prolonged post-ICU psychiatric morbidity in ARDS survivors [27]. Conversely, gender and age are not consistently associated with depression in post-ICU patients, differently from the general population, where female sex and people aged 40–59 years

are at greater risk. Illness severity and duration of ICU stay are also not associated with depression. This implies that screening programs should consider a large pool of ICU survivors of both sexes, all ages and with a wide spectrum of clinical severity [26]. Depressive symptoms are more often driven by somatic symptoms (i.e., bodily complaints such as pain, physical function limitation, dizziness, palpitations, fatigue) than cognitive–affective symptoms (i.e., thought-related and mood-related complaints) [28]. Somatic depression may have a partial response to psychopharmacological drugs [28] so that patients may not achieve complete remission, thereby reducing their compliance to treatment and increasing the risk of earlier relapse and a more severe and chronic course of illness. "Giving the patient a pill" is far too a simplistic solution to a complex problem. Instead, interdisciplinary care with physical and occupational rehabilitation, adequate treatment of pain and other somatic symptoms, and appropriate consideration of psychological distress and socioeconomic restraints should be considered together with psychiatric consultation and antidepressant drug therapy to achieve optimal care.

Prevalence of anxiety symptom in meta-analysis is 32% (95% CI 27–38%) at 2–3 months, 40% (33–46%) at 6 months, and 34% (25–42%) at 12–14 months [29]. Longitudinal studies with repeated assessment of the same population show no significant change in anxiety severity or prevalence over the first year after discharge [29]. As for depression, age and gender are not associated with anxiety symptoms, in contrast with studies in the general population, in which anxiety disorders are more common in women and people aged 30–44 years. Illness severity, length of ICU stay and ICU admission diagnosis are also not associated with anxiety. In ARDS, pre-morbid psychological distress immediately preceding acute disease onset has a strong association with prolonged post-ICU anxiety and depression psychiatric disturbances [27].

PTSD belongs to the "Trauma- and Stressor-Related Disorders" category in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and is the most common psychopathological consequence of exposure to a catastrophic event [30]. Diagnostic criteria include direct exposure to- or witnessing of- actual or threatened death, serious injury or sexual violence, intrusion symptoms, persistent avoidance of stimuli, negative alterations in cognition and mood, and severe alterations in arousal and reactivity with disturbed sleep and hypervigilance associated with the traumatic event. Duration of disturbance is longer than 1 month and causes significant distress or substantially impairs functioning. In ICU survivors, symptoms of severe PTSD occur in 22–24% of patients in the first 12 months post-ICU and are associated with substantially lower HRQoL. Prior psychopathology, benzodiazepine sedation and early memories of distressing ICU experiences are associated with PTSD. Of note, severity of illness, admission diagnosis, and duration of mechanical ventilation and ICU stay are not consistently associated with PTSD. Association with benzodiazepine might be spurious, possibly reflecting the increased need of anxiolytics in ICU patients with severe anxiety; however, this further emphasizes the need to sparingly use benzodiazepines and other sedative drugs and avoid deep sedation.

26.3 Conclusions

PICS is a major health problem for ICU survivors and their families and has a huge impact on patients' quality of life and the whole society. With decreasing ICU mortality observed in the last decades, the number of surviving patients is anticipated to increase, as is the number of those surviving with long-lasting severe functional, cognitive, and mental health impairments [31]. The list of symptoms and signs affecting patients surviving the critical illness is continuously updated, and it is a safe bet that PICS will soon need to widen its definition to include new conditions. The critical care community should consider it as a great priority to prepare the future generations of intensivists not only to save lives but also to take charge of PICS.

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Mechanical Ventilation in Limited Resource Settings

27

Theogene Twagirumugabe

27.1 Introduction

Mechanical ventilation in low resource Intensive Care Units (ICUs) is as essential, for the management of critically ill, as it is in high-resource settings, despite different challenges. In limited resource settings, indications for mechanical ventilation mostly consist in respiratory failure from various causes, airway protection in patients with decreased level of consciousness and circulatory failures with the aim of maintaining vital organs' functions. Unfortunately, in poor resource settings, not all areas and beds designated for ICU may be equipped with fully functioning ventilators. Therefore, the proportions of ventilated patients in low resource countries vary, owing to the discrepancy in availability of ventilators and to the difference in case-mix of admitted patients or in severity of the conditions motivating the admission in ICU [1–4].

Access to mechanical ventilation (MV) may contribute to a decline of critically ill patients' mortality in low resource ICUs, though the intervention can be jeopardized by complications, if all prerequisites are not fulfilled. Evidence on the practice of mechanical ventilation and on the outcome of ventilated patients is scarce in low resource countries. This chapter strives to unearth the limited existing evidence from those settings and to characterize the state of mechanical ventilation practice in those settings.

T. Twagirumugabe (✉)
University of Rwanda, College of Medicine and Health Sciences, Kigali, Rwanda

University Teaching Hospital of Butare, Huye, Rwanda
e-mail: twagirumugabe@chub.rw

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27.2 Facilities for Mechanical Ventilation in Limited Resource Settings

In resource-limited hospitals, an already limited ICU beds capacity is worsened by a lack of vital equipment for an appropriate management of critically ill, including ventilators. It is worth noting that less than 50% of available ICU beds in those settings are equipped with ventilators. In a survey conducted in Africa during 2020, respondents have shown that there is an average of 3.1 ICU beds per 100,000 people far below an average of 12.79 ICU beds in high income countries with some countries like USA and Italy having even more than 25 ICU beds per 100,000 people [5]. Moreover, not all ICU beds in Africa are equipped with ventilators and this was estimated to 0.97 ventilators per 100,000 people. This gap was more important in African low-income countries with only 0.53 ICU bed and 0.14 ventilators for 100,000 people compared with 2.49 ventilators in African upper middle-income countries and the existing ventilators are mostly concentrated in urban areas, leaving remote and rural areas with almost no means to care for patients in such needs [1, 2]. This limited access to respiratory support in limited resource settings may have a much more negative impact in tertiary level or referral health facilities as nearly 80% of patients admitted to their ICUs are likely to require the mechanical ventilation [4]. This brings an ethical challenge to providers of selecting who should be admitted and ventilated. This is a psychological burden on staff, in a setting where personnel qualified to take care of critically ill patients is badly lacking. This complexity is further worsened by an erratic availability of necessary basic infrastructure for an effective use of ventilators, such as permanently uninterrupted electricity and appropriate oxygen systems [6, 7].

The gap in ventilators and limited ICU capacity is a long lasting reality in limited resource countries, which vibrantly arose during the current COVID-19 pandemic. Some industries, in collaboration with western universities, initiated projects to design and manufacture economically affordable and easy to use ventilators, also for resource-limited settings. However, important pieces of the puzzle seemed to be overlooked or at least not given an appropriate attention [8–10]: these include the appropriate oxygen production (or supply), training of skilled engineers for the maintenance of these ventilators and a decent training of end-users. In fact, from a survey conducted in 2010 by WHO in 12 Western and Eastern African countries, only 43% of health facilities had access to oxygen, which was only contained in cylinders or produced by oxygen concentrators and the uninterrupted electricity was barely available in one-third of surveyed facilities [11]. The situation had probably not changed much 10 years later, as it has been proven during the COVID-19 pandemic [10].

27.3 Indications of Mechanical Ventilation in Resource Variable Settings

The main reasons for admission and indications for mechanical ventilation in limited resource ICUs, similarly to the rest of the world, are sepsis and septic shock, trauma, poisoning, postoperative for recovery, and peri-partum complications with

Table 27.1 Kigali modification of the Berlin definition of ARDS [14]

	Berlin criteria	Kigali modification of the Berlin criteria
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	$PaO_2/FiO_2 \leq 300$	$SpO_2/FiO_2 \leq 315$
PEEP requirement	Minimum 5 cm H_2O PEEP required by invasive mechanical ventilation (non-invasive acceptable for mild ARDS)	No PEEP requirement
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT scan	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound
Origin of pulmonary oedema	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)

PEEP positive end-expiratory pressure, SpO_2 peripheral saturation of oxygen measured by pulse oximetry, PaO_2 arterial partial pressure of oxygen measured by blood gas, FiO_2 inspired fraction of oxygen, *CT* computed tomography

some variations between settings [3, 12, 13]. The acute respiratory failure in its extreme presentation, as acute respiratory distress syndrome (ARDS) has been missed for long, owing to the inaccessibility to the diagnostic criteria, but by using the Kigali modification of Berlin definition of ARDS (Table 27.1), it has been shown that ARDS is also an existing entity in limited resource settings, in proportions relatively similar to high-resource settings [14, 15]. However, only one-third of patients with ARDS (or high suspicion of) can be admitted in ICU, given the limited bed capacity [14]. One might also assume that, with the lack of recognition of the condition, patients with ARDS may not benefit from an appropriate management, with a particular emphasis on ventilator's parameters, which might cause harm to patients and increase their mortality.

27.4 Modes of Mechanical Ventilation in Limited Resource Settings

The classic invasive mechanical ventilation (IMV) through tracheal intubation, as opposed to non-invasive ventilation (NIV), that does not require this intubation might be expected to be the most prevalent, in limited resources settings, given the indications to mechanical ventilation [3, 12, 13]. However, invasive ventilation is technically more resource-demanding, with a need of sedation and a presence of an experienced anaesthesia provider for intubation and anticipation cardiorespiratory complications, that may occur in about 40% of cases [16]. In limited resource facilities, the IMV can, therefore, be associated with an increased mortality among

ventilated patients, but well-designed studies, taking into consideration severity of the patient to allow objective comparisons and establish attributable mortality are lacking. The high mortality observed with IMV is sometimes used as an argument to favour the use of the non-invasive ventilation (NIV) as a safer alternative for respiratory support in low resource settings, but not all patients qualify for it [17].

NIV may indeed be considered as an interesting option, since it allows to avoid potential complications deriving from intubation. Moreover, when initiation of IMV is decided, NIV can also be a way to prevent some of the complications related to intubation, being used for pre-oxygenation. In appropriately selected patients with acute respiratory distress following acute cardiogenic pulmonary edema and/or acute exacerbation of COPD, NIV can be the sole and effective option for respiratory support in such cases [18]. NIV has also been evaluated in the management of ARDS patients during the first 48 h from diagnosis, but failure rates increased with severity of the hypoxemia and patients with severe ARDS treated with NIV modality were at significantly higher risk to ICU mortality [19].

In limited resource settings, neither the indications nor the outcome of NIV are known. However, the availability of NIV facilities and equipment in those setting has been reported in different studies but mainly in university-affiliated hospitals [20, 21].

Different devices, other than full-face mask, such as nasal mask, helmet and the high flow nasal cannula are basically not documented in limited resource settings.

Evidence on the experience of NIV in those settings is limited to the use of the basic bubble low flow CPAP mainly in neonatal and paediatric patients, among which this technique seemed to bear an improved outcome [22, 23].

The experience with other NIV modalities or interfaces and their advantages over the IMV is poorly reported (if not at all) in limited resource settings.

27.5 Complications of Mechanical Ventilation in Limited Resource Settings

NIV and, to greater extent, IMV can be burdened by various complications. Ventilation-associated complications or events can arguably be reliable metrics of the quality of care around MV. Indeed, majority of the complications can be avoided by appropriately setting ventilator parameters, according to the lung mechanics' abnormality in the context specific of a given patient. Ventilator-induced lung injury (VILI) is a well described complication that may result from the non-adaptation of the patient's spontaneous breathing mechanics to the ventilator and/or the ventilator's parameters' set up that are not suited for the pathophysiological pattern of the condition requiring this respiratory support. VILI are therefore likely more important in limited resource settings due to the lack of skilled personnel in ICUs. Through the different mechanisms as volutrauma, barotrauma, atelectrauma or biotrauma, the VILI are in fact important in low resource facilities but the evidence on their incidence, pathogenesis and impact on the patients' outcome remains scarcely explored and reported [24].

VILI can be limited by the application of Lung Protective Ventilation, including low tidal volume, a limited plateau pressure, and an optimal PEEP, but the compliance with this in limited resource settings is unknown. However, a study conducted in ICUs from 10 Asian middle-income countries has revealed a modest-to-good compliance with this best practice in those settings [21]. Whether the lack of compliance with this strategy in low resource countries' ICUs of Africa for instance is contributing to the higher morbidity and mortality of ventilated patients is unclear [13].

Beside VILI, another serious and most prevalent complication of MV is ventilator-associated pneumonia (VAP). The rates of VAP among mechanically ventilated patients increase with the duration of the ventilation and VAP are more prevalent in low resource settings with up to almost 116 per 1000 ventilator days, with this incidence being much higher in settings of sub-Saharan African countries [25, 26]. VAP carries an increased burden of mortality of ventilated patients, especially when multi-drug resistant microorganisms are involved and, most importantly, when these are carbapenem-resistant [26, 27].

One of the reasons behind these high VAP rates is the modest adherence to the "ventilator bundle" (helping to reduce the incidence of VAP) in middle-income countries [21] and possible in low-income countries, but data are lacking.

Another strategy to reduce VAP's incidence, with a perspective to shorten the duration of mechanical ventilation relies on the preventive tracheostomy, which allows an appropriate oral hygiene, oral feeding, and avoiding continuous laryngeal trauma.

27.6 The Practice of Tracheostomy in Patients with Prolonged Mechanical Ventilation

Early tracheostomy, performed at the end of the first week of MV, might be associated with a shortening of MV duration, hospital length of stay and, possibly, a reduction in VAP incidence. However, the impact on ICU and hospital mortality is still unclear [28].

Existing data on tracheostomy in patients with prolonged MV in low resource ICUs show that the vast majority perform a late tracheostomy and the intervention is followed by a high rate of complications including tracheal stenosis in up to 40% of cases and no impact on ICU and hospital mortality [29, 30].

27.7 Conclusion

The practice of mechanical ventilation in limited resource settings relies mainly on IMV but some facilities for NIV are available in university-affiliated hospitals, though this approach mainly consists in the application of bubble CPAP among paediatric population.

Even if the indications of MV are probably different from higher-resource countries, patients with ARDS (or at risk of) do exist in limited resource settings. The compliance with the lung protective strategy in those patients is modest-to-good in middle-income settings but not documented in low resource ones.

Mechanical ventilation is complicated with a high rate of VAP and patients with prolonged MV undergo late tracheostomies that are in turn tarnished by a high rate of post-extubation tracheal stenosis.

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Mechanical Ventilation During Patient's Transferral

28

Susan Wilcox and Raymond Che

28.1 Overview

The transport of mechanically ventilated patients is complicated, involves extensive preparation, requires skilled personnel, and carries a risk of adverse events [1–6]. Maintaining the patient's clinical status, or even improving it, requires significant resources from the transporting and receiving institutions [7]. Therefore, the benefits of transport must outweigh the risks [3, 4, 7, 8]. In addition to recognizing risk factors, transport with highly skilled clinicians can mitigate adverse events [1–11]. While it is important to realize the differences between intra and inter-hospital transfers, the principles in this chapter can be applied to both scenarios.

28.2 How Transport Changes Physiology

Three main mechanisms affect a patient's physiology during transport. The first is the movement of the patient, including transferring beds, changes in positioning, and acceleration/deceleration. Patients with hypoxemic respiratory failure may have tenuous ventilation/perfusion (V/Q) matching, often with large areas of shunt. Movement can cause redistribution of the blood flow to less well-ventilated areas, overcoming hypoxemic vasoconstriction-based matching and resulting in desaturations. In fact, 28% of patients with hypoxemic respiratory failure have been shown to desaturate in transport [12].

S. Wilcox (✉)
Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA
e-mail: swilcox1@partners.org

R. Che
Arkansas College of Osteopathic Medicine, Fort Smith, AR, USA

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The second includes any abrupt changes in the patient's support, such as short-term discontinuation of pumps or swapping to a transport ventilator. Even a simple change in the environment can lead to stress and discomfort to the patient [2]. Clinicians can minimize the impact of these changes with good practices, such as ensuring that medications are ready to be swapped out or that the transport ventilator is set-up prior to changing. Given that the typical patient population who is transported are already at high risk for in-hospital mortality, clinicians should minimize these factors to reduce physiologic compromise during transport [9].

Lastly, if the patient is to be transported by air, changes in atmospheric pressure may impact their oxygenation. With increasing altitude, the partial pressure of oxygen decreases. This results in a decrease in the pressure differential required for oxygen to diffuse across the alveoli. An oxygen saturation of 98% at sea level will decrease to 87% at 10,000 ft (3048 m) [13]. Additionally, the decreased partial pressure results in fewer oxygen molecules being inhaled with each breath. As such, breathing ambient air at 8000 ft (2438 m) is equivalent to breathing 15% oxygen at sea level.

Fixed-wing transports usually pressurize the cabin to about 8000 ft. However, helicopter transports are not typically pressurized. For patients without baseline respiratory failure, flying in a helicopter does not usually cause clinically significant changes. However, patients who are already hypoxemic may experience significant deteriorations.

Additionally, Boyle's law states that the volume of a gas is inversely proportional to the pressure to which it is subjected. Atmospheric pressure decreases with increased altitude, thereby causing the expansion of gases. This can result in expansion of pneumothoraxes and decreased functional residual capacity due to bowel gas expansion.

28.3 Setting the Ventilator for Transport

While transport ventilators vary, most models allow ventilator settings and monitoring similar to ICU ventilators. To maintain care commensurate or higher than that of the sending facility, as is the goal of critical care transport, a ventilator should provide all common modes, included Assist Control—Volume Control Ventilation or Pressure Control Ventilation, Pressure Support, and any other used modes by regional variation. All transport ventilators can provide positive end-expiratory pressure (PEEP), although many are limited to 20 or 22 cmH_2O. The fraction of inspired oxygen can be adjusted, and the respiratory rate can be set, depending upon the mode. The peak inspiratory pressure (PIP) can be monitored, although the ability to measure a plateau pressure varies by brand. Most allow monitoring of autoPEEP as well.

For most patients, a lung protective, low-tidal volume, low pressure strategy is appropriate [8]. Although there are no trials of ventilator management in transport, work has shown that the transport tidal volume impacts tidal volumes in the receiving emergency departments and intensive care units [14]. Targeting 6 mL/kg of

predicted body weight and a driving pressure of less than 15 cmH_2O is appropriate in most situations. The PEEP can be titrated by oxygenation and the patient's compliance. Given the propensity for instability in transport, patients may require an increase in their FiO_2. Titration of settings is performed frequently at the team's discretion; however, the number of patients left on inappropriate ventilator settings ranges from 5% to 32% [2, 11]. Transport teams have the opportunity to positively impact ventilation settings by appropriately lowering tidal volumes, increasing PEEP, and increasing FiO_2. However, to do so, personnel must be trained and prepared to make correct ventilator adjustments en-route.

28.4 Pulmonary and Airway Complications

Hypoxemia is the most recognized complication of transport, affecting up to 29% of transported patients [1]. This can be attributed to secretions that are mobilized by movement, changes in patient position, or loss of PEEP [2, 5]. These effects of movement can increase the risk for atelectasis up to threefold during transport [4]. This highlights the importance of suctioning to improve oxygenation, reduce atelectasis, decrease ventilator pressures, and possibly reduce the risk of ventilator associated pneumonia. Patients requiring a PEEP greater than 6 cmH_2O, or FiO_2 greater than 0.5 have generally been considered a high-risk group to transport, as these are associated with increased risk of oxygenation complications [2, 4, 7]. FiO_2 is frequently increased during transport to provide a safety net or temporarily address a patient's respiratory deterioration without considering the pathophysiology and addressing the root cause. This practice can potentially further contribute to de-recruitment via absorption atelectasis. Another option available to practitioners is to consider a higher level of PEEP, titrated to the individual patient, as the application of PEEP has historically been conservative among transported patients [11].

Hyperventilation occurs frequently with the use of manual ventilation devices, such as bag-ventilation. As such, transporting clinicians should use mechanical ventilation with set parameters whenever possible. Avoidance of manual ventilation with bagging is a quality metric for many transport organizations. Anxiety, pain, and movement during transport can result in the patient triggering additional breaths on mechanical ventilators. Thus, adequate sedation should be prioritized, especially if the patient is dyssynchronous with the ventilator.

In addition to sedation, neuromuscular blockade (NMB) is utilized often for transport [2, 7, 11]. Prior work found that NMB was associated with improved 90-day mortality in patients with moderate to severe ARDS. However, a larger, more recent trial found that NMB is not associated with a mortality benefit [15]. As such, NMB is no longer routinely recommended in the management of hypoxemic patients. However, when patients are dyssynchronous despite sedation, NMB is appropriate to reduce the risk of ventilator-induced lung injury. Many transport organizations will use NMB after adequate sedation for high-risk transports to reduce one potential variable for risk–patient-generated movement. In addition, the

administration of NMB in transport has been associated with improved oxygenation [7].

Hypoventilation can occur secondary to airway displacement, occlusion, or malpositioning, which is a risk of transporting patients [2]. Second, sedation or neuromuscular blockade paired with inadequate ventilator settings can result in hypoventilation. When transport teams reduce tidal volumes to reduce the risk of ventilator-induced lung injury, they must also increase the respiratory rate to maintain the minute ventilation. Prior work has shown that increasing the respiratory rate may be forgotten in transport, resulting in worsening respiratory acidosis [7]. It is important to note that many pulmonary complications are commonly attributed to equipment malfunction and human error [4].

28.5 Cardiovascular Complications

Hemodynamic changes remain the most frequently encountered complication during transport. Hypotension is the most common, followed by non-trivial changes in heart rate and arrythmias [1, 4, 6, 11]. Hypotension is common with movement due to fluid shifts, and experientially, the higher the patient's pressor requirements, the greater the risk of substantial deterioration with motion. Expanding pneumothoraces, while rare, can lead to hypotension [4]. Conversely, stress, pain, and anxiety can result in hypertension, emphasizing the importance of maintaining adequate sedation during the patient's retrieval. Cardiac arrest is a rare but catastrophic event during transport. Many cases are attributed to inadequate monitoring of the patient secondary to unsupervised or untrained staff [4, 6, 7].

28.6 Equipment Malfunction, Considerations, and Human Error

Equipment malfunction or inadequately trained staff are also significant contributors to critical events during transport [1, 2]. Examples include ECG lead failure, monitor failure, loss of intravenous access, and ventilator disconnections [4]. The occurrence of adverse events is dependent on team composition and caliber of expertise. Specialized physician presence may significantly reduce the risk for adverse events when staff with appropriate training are not available [1]. On the other hand, a skilled team with specialized training and the capability for remote physician consultation reduces risk. Regardless of the discipline of the members of the transport team, all must recognize that transport medicine is a specialized medical practice. The resources of the hospital are not available, and the team must

contend with the effects of motion while maintaining both patient and crew safety. As such, clinicians should not be sent on transports without proper training or supervision in the transport environment, regardless of their clinical expertise. It is important to develop a transport system in advance to allocate the appropriate staff and resources to meet patients' needs [10].

Inadvertent disconnection of the patient from the ventilator can occur from the circuit catching during movement [4]. Although usually caught quickly, disconnecting high acuity patients from the ventilator, even for brief intervals, can cause de-recruitment leading to V/Q mismatch that may require increased ventilator parameters to reverse. Continuous End Tidal CO_2 monitoring is an excellent (and underused) tool for monitoring ventilator and airway status, as it can immediately detect ventilator failure and unplanned extubation [2]. It is important to factor the patient's tolerance to being disconnected to the ventilator when planning transport.

28.7 Importance of Checklists

The best method of reducing the risk of adverse events is the adoption and strict adherence to a systematic checklist [1–4, 10]. The checklist can be divided into three distinct phases of the transport process: (1) pre-transport, (2) transport, and (3) post-transport. Each phase can then be subdivided into four more categories: (1) organization and planning, (2) monitoring equipment, (3) physiology, (4) medications [1]. An example of a pre-transport checklist is shown in Table 28.1.

During the pre-transport phase, the patient should be evaluated for any contraindications for transport which includes failure to establish and maintain an airway, or insufficient monitoring resources. At this time, a risk-vs.-benefit ratio should be assessed. Once the decision is made to transport, a minimum of two qualified staff (not including vehicle operators) must be selected based on the acuity of the patient. Communication (nurse–nurse and physician–physician) between the transporting and receiving institution should be made. Appropriate equipment/monitoring devices should be accounted for, and function tested. The patient is then be prepped for transport with lines reorganized, airway secured, and medications within easy access. During the transport phase, the priority is to ensure the patient remains stable by maintaining ICU level care, and continuously monitoring vitals. Upon arrival at the receiving hospital, i.e., the post-transport phase, the patient must be placed back on ICU equipment. A detailed report of vitals, medications administered, events, and interventions should be given. Equipment should be cleaned, charged, and prepared for the next use [1–3, 10].

Table 28.1 Example of Pre-transport checklist

Pre-transport ventilator checklist	
	Verified or value
Organization and planning	
Pre-transport logistics	
Necessity of transport confirmed	
Patient identification confirmed	
Receiving facility notified	
Pre-transport patient assessment performed	
Baseline vitals recorded	
Monitoring equipment	
Airway	
ETT placement confirmed/depth recorded	
Airway secured with tube holder or tape	
Emergency/difficult intubation kit	
Surgical airway kit	
Spare tracheostomy cannula/obturator (if applicable)	
Ventilator equipment	
Spare circuit	
Spare HME	
Full battery/spare/charger	
In-line suction and spare	
$ETCO_2$ monitor	
Oxygen cylinders full and spares	
Manual resuscitation device with PEEP valve	
Physiology	
Ventilator parameters	
Initial settings confirmed with sending	
Recent blood gas values	
Predicted body weight (PBW)	
Exhaled Vt in mL/kg PBW	
Minute ventilation value	
Plateau pressure <30 cmH_2O	
Alarms set	
Trigger setting appropriate	
Medications	
Medications and equipment	
Sufficient IV medications	
Additional sedatives/analgesics	
Vasopressor/inotropic agents	
Spare infusion pump	
Spare IV fluids	

28.8 Conclusion

The process of patient transport involves assessing a patient's risk factors, a clear understanding of the benefits, and careful implementation of standardized checklists. Equipment must coincide with the patient's needs. While the patient's physiologic conditions are complex and are factors that cannot be resolved prior to transport, understanding the most frequent complications and extra training to prepare personnel to deal with these situations as they arise during transport.

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Part III

Adjuncts to Mechanical Ventilation

Prone Position

29

Claude Guérin

Prone position has been used for almost 50 years from now (Fig. 29.1) and has received further appraisal with the COVID-19 pandemic. Indeed, the rate of use of prone position jumped from 10 to 30% in the classic Acute Respiratory Distress Syndrome (ARDS) [1, 2] to more than 70% in the COVID-19-related ARDS [3]. This finding was observed when the level of evidence was the same during the two periods. This chapter will cover the rationale, the timing, some practical issues, and the clinical results, including those observed during the COVID-19 pandemic, of using prone position.

29.1 Rationale

From achieving a better oxygenation in intubated ARDS patients with severe hypoxemia the rationale to indicate prone position has embedded the prevention of ventilator-induced lung injury (VILI). Furthermore, the fact that prone position preserves and can even improve cardiac output has been recently emphasized.

29.1.1 Effects on Oxygenation

The mechanisms by which oxygenation improves, sometimes dramatically, following proning, are important to take in consideration. Oxygenation improvement with

C. Guérin (✉)
Médecine Intensive-Réanimation, Hôpital Edouard Herriot, Lyon, France

Université Claude Bernard Lyon I, Lyon, France

Institut Mondor de Recherches Biomédicales INSERM U955, CNRS 7200, Créteil, France
e-mail: claude.guerin@chu-lyon.fr

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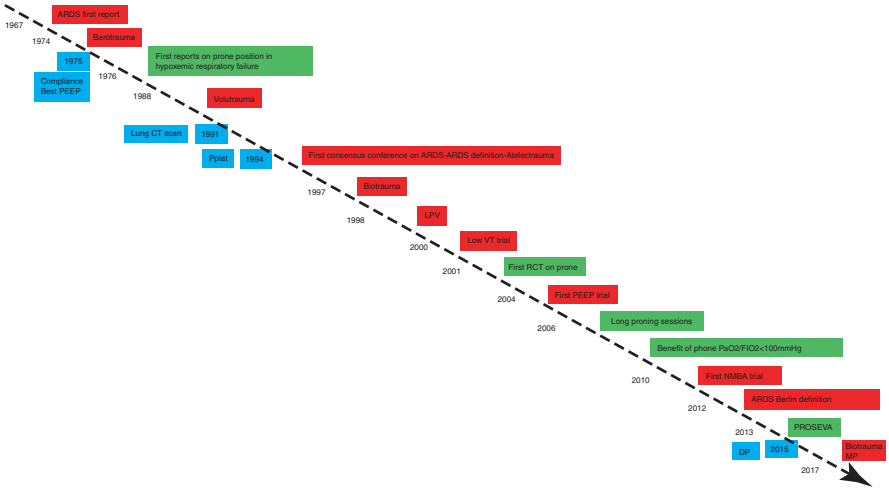

Fig. 29.1 Schematic drawing over time (not scaled) of some of the main steps in the acute respiratory distress syndrome (ARDS) management. Red boxes highlighted the mechanical ventilation, blue boxes the physiological monitoring and green boxes the prone position. *Pplat* plateau pressure, *LPV* lung protective ventilation, *PEEP* positive end-expiratory pressure, *DP* driving pressure, *RCT* randomized controlled trial, *VT* tidal volume, *NMBA* neuromuscular blockade agent, *MP* mechanical power

proning results from a reduction in intra-pulmonary shunt and a better ventilation-to-perfusion matching. The basic and typical scenario involves an increase in lung ventilation in the spinal, nondependent, parts of the lung, which continue to receive most of the pulmonary blood flow (at least in non-COVID-19 ARDS). Indeed, prone position promotes lung recruitment (lung tissue which gets aerated) in the dorsal lung regions, but does not significantly redistribute the pulmonary blood blow away from them. A scenario like this should also result in lower $PaCO_2$. Prone position enhances the beneficial effect on oxygenation of inhaled nitric oxide.

29.1.2 VILI Prevention

As the oxygenation goal should target modest objectives and the fact the VILI prevention came in as the main goal in delivering mechanical ventilation in ARDS, the central role of better oxygenation was less prominent, yet prone position still kept up the deal. Suggested by a landmark CT scan study that measured the lung gas-to-tissue ratio [4], the overall lung stress (i.e., the trans-pulmonary pressure) and strain (and its surrogate the driving pressure) is reduced in prone and, as importantly, its distribution throughout the lung is made more homogeneous [5] (Fig. 29.2). That means that the tidal volume is associated with a lower risk of over distending the baby lung, everything else being equal. For a given tidal volume, positive

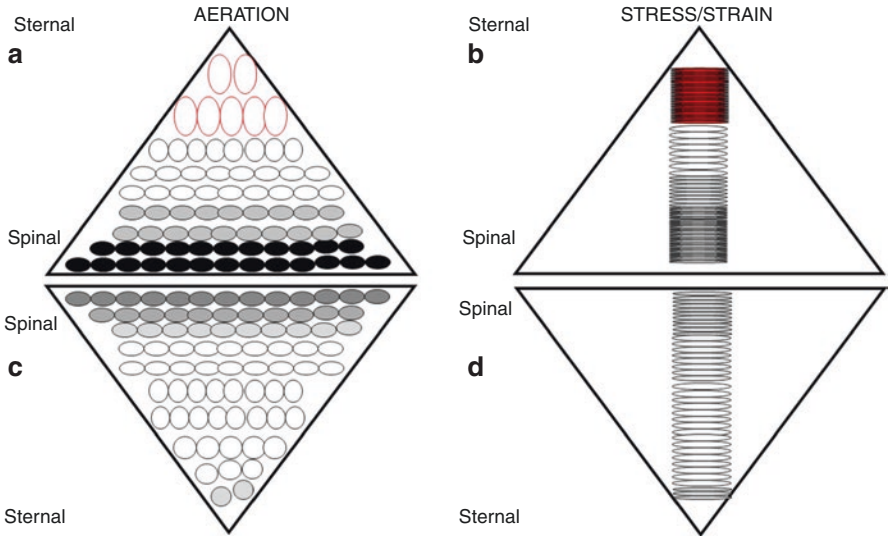

Fig. 29.2 Schematic drawing of the distribution of lung aeration and lung stress/strain in an ARDS lung in supine (**a**, **b**) and in prone position (**c**, **d**). The black ellipses are consolidated lung regions that do not experience stress because they are not ventilated. The gray ellipses are partially aerated lung regions. Those partially aerated lung regions that are close to the consolidated ones have a very high stress while those which are more distant have a lower stress but higher than normal. The white ellipses are normally aerated lung regions, i.e., the baby lung, with quite normal stress. Finally the white ellipses surrounded in red are overdistended lung regions and share a high stress. When turned to prone position there is both a lung recruitment and a reduction of overdistension. The overall lung stress/strain is reduced and its distribution is made more homogeneous across the lung

end-expiratory pressure (PEEP) does not significantly change the distribution of strain [5]. Proning increases the chest wall elastance from the supine at 0° inclination of the body [6]. Therefore, the change in respiratory system elastance may not reflect the change in lung elastance. For the lung elastance to decrease in prone, and then heralding lung recruitment, its reduction should be higher that the increase in chest wall elastance making the elastance of the respiratory system possibly unchanged. An increase in chest wall elastance, as it reduces lung overdistension, may also protect the lung [7].

29.1.3 Hemodynamics Effects

Proning can unload the right ventricle as a result of lowering pulmonary vascular resistance, via better gas exchange and increase in end-expiratory lung volume. More recently it has been shown that prone position can increase the cardiac output, in particular in preload-dependent patients in supine position [8].

29.2 Timing of Proning Application

29.2.1 PaO_2/F_IO_2 Threshold to Initiate Proning in ARDS

Stemming from an individual meta-analysis of four multicenter trials, the benefit of proning was suggested in ARDS patients with a PaO_2/F_IO_2 ratio < 100 mmHg at the time of randomization [9] (Table 29.1). This threshold was confirmed by experts [10]. However, a trial performed afterwards in moderate-to-severe ARDS patients included at PaO_2/F_IO_2 < 150 mmHg demonstrated a significant reduction in mortality up to 90 days after inclusion [11] (Table 29.1).

29.2.2 When to Start Proning

The PROSEVA trial [11] mandated a 12–24 h stabilization period before including the patients and, once included, the patient in the prone group were to be proned within the next 1 h. This aimed to proning the patient early after having made every effort to confirm the ARDS. At the same time, patients with an immediate indication of proning for extremely severe hypoxemia or those with a rapid improvement were not included. However, an early proning after ARDS recognition, stabilization and confirmation was efficient and safe. In the COVID-19 pandemic an early use of prone, i.e., within the 2 days after intubation, was associated with a better outcome as compared to a later proning in a large observational database [12]. The prone position-induced lung recruitment in the dorsal lung regions was significantly greater when pigs were proned early (day 1 after ARDS) than late (day 2) [13].

Table 29.1 Five large randomized controlled trials comparing prone to supine position in acute respiratory distress syndrome

First author	Italy	France	Spain	Italy	France and Spain
N patients (SP/PP)	152/152	378/413	60/76	174/168	229/237
% of ARDS (SP/PP)	93.3/94.7	28/33.9	100/100	100/100	100/100
PaO_2/FIO_2 (mmHg)	127	150	147	113	100
Tidal volume (mL/kg)	10.3 MBW	8 MBW	8.4 PBW	8 PBW	6.1 PBW
PEEP (cmH_2O)	10	8	12	10	10
PP hours per session	7	8	17	18	17
Mortality (SP/PP) (%)	25/21.1	31.5/32.4	58/43	32.8/31	32.8/16

Definition of abbreviations. *SP* supine position, *PP* prone position, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *MBW* measured body weight, *PBW* predicted body weight

29.2.3 When to Stop Proning

The timing to stop proning is as crucial as its initiation. In the PROSEVA trial [11] predetermined criteria based on oxygenation, PEEP and F_IO_2 were a priori defined in supine position. So, the definition of responders to prone in terms of oxygenation was defined by comparing supine pre-prone to supine post-prone, and not by considering the oxygenation change during the proning session. That means that proning was continued even though these criteria were not met, i.e., whether or not the patient exhibited an excellent oxygenation response or no change at all. A safety guard was that proning was stopped when oxygenation deteriorated by more than 20% over two consecutive sessions. This strategy aimed at setting the benefit of prone primarily from VILI prevention rather than oxygenation improvement. This issue is probably very important and led to some confusion in the literature, but also in practice. In the classic ARDS, there were no solid data showing that responders (in terms of oxygenation improvement) to prone did better than the nonresponders. A post-hoc analysis of the PROSEVA trial found no correlation between patient outcome and early or late response to prone in terms of PaO_2 or $PaCO_2$ [14] in line with a previous study by others [15]. However, in COVID-19 ARDS two observational studies suggested a significant association between oxygenation response and patient outcome [16, 17].

29.2.4 Duration of Proning Sessions

The three last trials done in Spain, Italy, and France used prolonged proning cycles, very much greater than 12 consecutive hours [18]. The rationale for long sessions is to minimize the occurrence of changing position for practical issues, having in mind nevertheless that changing position is a component of the proning treatment. Another rationale is more physiological: assuming that proning attenuates VILI, the longer the prone is applied the higher the likelihood of less VILI during mechanical ventilation. Extended use of proning in COVID-19 has been found feasible and effective [19].

29.3 Practical Issues

29.3.1 Patient Installation

In the large majority of the cases the use of patient's own bed and mattress and 3–4 caregivers with a mandatory one at the patient's head to control the artificial airway allows to make it. The COVID-19 with the large amount of patients who were proned, the prevalence of obese patients who were proned and the use of prone under ECMO challenged the nursing team and the devices as well. Exosquelettons attached at both the patient and the caregiver have been used to facilitate the procedure and increase its safety, and to reduce the injury to the caregivers [20, 21].

29.3.2 Support of Abdomen

Whether or not the abdomen should be supported is not definitely answered. A non-supported abdomen is recommended during late pregnancy together with the fetus heart rate monitoring.

29.3.3 Sedation and Neuromuscular Blockade During Prone Position

Most of the ARDS patients in prone position receive continuous intravenous both sedation and neuromuscular blockade [22]. The use of a minimal sedation with no neuromuscular blockade in ARDS even in prone position is a current hot topic but there is no published study on sedation in proned ARDS patients with or without neuromuscular blockade.

29.3.4 Setting the Ventilator in Prone Position

Resulting from better oxygenation the common ventilator setting change is a reduction in FIO_2 in prone. The frequent question about how to set PEEP in prone is still open. In the PROSEVA trial [11], PEEP was driven by a PEEP-F_IO_2 table and was reduced in prone, making the prone a-PEEP-sparing strategy. This may have contributed to 2 days with cardiovascular organ dysfunction less than in the supine group. Two other considerations would argue for higher PEEP in prone, one is the increase in chest wall elastance in prone and the other the lung recruitment. Indeed, if prone had induced lung recruitment, when the patient went back to supine higher PEEP should be set according to the "open the lung and keep it open" concept. Guiding PEEP setting by using esophageal pressure would be an attractive strategy as the relevance of esophageal pressure would be better in prone than in supine assuming that compression of the sensor by the gravity and the weight of lung, mediastinum and heart would be less. However, for a given end-expiratory transpulmonary target and as compared to the same baseline PEEP, the use of esophageal pressure did not result in a significant change in PEEP in prone as compared to supine [23]. However, it allowed to titrate the PEEP level at the individual patient level.

29.3.5 Contraindications

The single remaining absolute contraindication to proning in ARDS is an unstable spine fracture [18]. The followings are relative contraindications to be discussed on a case-by-case basis evaluating the risk-to-benefit ratio: shock, elevated intracranial pressure, surgical or medical abdominal problem. Obesity, even morbid, is not a

contra-indication as obese patients should benefit from proning given the important closing volume that should be relieved in prone, together with a judicious PEEP selection. As a matter of fact pregnancy is not a contra-indication to prone position as discussed above.

29.4 Clinical Evidence

29.4.1 Effects of Survival in Intubated Patients with Classic ARDS

As mentioned, several trials comparing supine to prone position did not find any significant outcome benefit but an individual meta-analysis resulted in the first positive signal favoring the use of proning in the most hypoxemic patients [18]. Then, the PROSEVA trial was the first one to demonstrate a significant outcome improvement with prone position, and, hence what is evidence-based is the prone position in ARDS patients with PaO_2/F_IO_2 ratio < 150 mmHg. This threshold received a conditional recommendation by experts [10] and a strong recommendation by others in the classic ARDS [24]. It was also recommended during the COVID-19 pandemic [25].

29.4.2 Findings in the COVID-19

The studies on pathophysiology of COVID-19-related ARDS pointed out two main findings: (1) a discrepancy between hypoxemia severity and preserved lung aeration reflected by better compliance of the respiratory system than in classic ARDS, (2) an involvement of the pulmonary circulation (microthrombi in the lung capillaries, impairment of hypoxic pulmonary vasoconstriction) making the redistribution of pulmonary blood blow with PEEP and also with prone position different from and the dead space higher than in the classic ARDS. However, the management of COVID-19 ARDS was recommended not to be different from the classic ARDS, including the use of prone position, which, as previously mentioned, exploded. Another trait was the massive use of prone position in awake non-intubated patients with severe COVID-19 pneumonia, not only in the intensive care unit (ICU) but also in the emergency room and in the ward. The goal was to spare the rare ICU resources, of utmost importance for the most severe patients. By doing so, the clinicians expected an improvement in oxygenation that would allow to buy time and to avoid intubation. This strategy was particularly used in developed countries, which experienced oxygen shortage. The risk was to delay intubation. Several trials have been conducted testing whether prone position, against supine, can avoid intubation and reduce mortality in awake non-intubated patients with a severe COVID-19 pneumonia. We are waiting for the final results of them. It should be mentioned that prone position in awake patients might be lung protective if it can reduce the patients' inspiratory effort and hence the trans-pulmonary pressure.

29.5 Conclusions

Prone position should be used in ARDS patients with a PaO_2/FIO_2 ratio < 150 mmHg if there is no contraindication. The COVID-19 clearly showed that the clinicians adopted this strategy even though the level of evidence was the same as before the pandemic. It remains to establish if this infatuation will continue when the pandemic is over.

Further studies are required to demonstrate if prone position can improve outcome in ARDS patients with PaO_2/F_IO_2 > 150 mmHg (a trial is in preparation in France), if prone position should be selected in responders, which requires a standardization of the response to prone, and if awake prone position has a role also outside COVID-19.

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Veno-Venous ECMO and $ECCO_2R$

30

Marco Giani, Christophe Guervilly, and Giuseppe Foti

30.1 Pathophysiology of Severe Respiratory Failure: Pulmonary Shunt and Alveolar Dead Space

Patients suffering from the most severe form acute respiratory distress syndrome (ARDS) present with life-threatening hypoxemia and/or respiratory acidosis. The ARDS lung shows complex histopathological alterations, including alveolar flooding, alveolar collapse and microvascular thrombosis [1]. These alterations result in shunt and dead space, which lie at the two opposite limits of the ventilation–perfusion relationship. Shunt occurs in alveolar-capillary units which are perfused but not ventilated, and is responsible for hypoxemia refractory to increased inspiratory oxygen (FiO_2) fraction.

In the presence of shunt, the ventilated regions are relatively underperfused. This, in adjunct to the microvascular thrombosis determines the increase of alveolar dead space, which result in the requirement of high minute ventilation to remove carbon dioxide (CO_2) from blood, due to the "waste" of mechanical ventilation in alveoli which are not perfused.

M. Giani (✉) · G. Foti
School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

ASST Monza, Emergency and Intensive Care, Monza, MB, Italy
e-mail: marco.giani@unimib.it; giuseppe.foti@unimib.it

C. Guervilly
Medical Intensive Care Unit North Hospital, APHM, Marseille, France

CER-eSS, Center for Studies and Research on Health Services and Quality of Life EA3279, Aix-Marseille University, Marseille, France
e-mail: christophe.guervilly@ap-hm.fr

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30.2 Why Extracorporeal Gas Exchange?

Since more that 40 years, veno-venous extracorporeal membrane oxygenation (V-V ECMO) has been described as an effective rescue therapy to replace the gas exchange function of the failing lung [2, 3]. The rationale of extracorporeal gas exchange relies on providing oxygenation, CO_2 removal and to drastically decrease the ventilation of the native lungs. In a way, V-V ECMO is a "symptomatic" treatment that buys time for the lung to heal.

V-V ECMO may be used either as a rescue therapy for hypoxemia [2], or to decrease ventilatory load by the extracorporeal removal of CO_2 ($ECCO_2R$) [4–6]. To achieve the first goal, a high-flow veno-venous extracorporeal support (i.e., 3–6 L/min of blood flow) is required to provide adequate oxygenation. Contrarily, $ECCO_2R$ requires only a low extracorporeal blood flow (i.e., 500–1500 mL/min) due to higher solubility and diffusion through the membrane lung of CO_2 as compared with O_2 [7]. Eventually, this may correct or prevent respiratory acidosis, thus reducing the ventilatory burden. This divergence is secondary to the different physiology of O_2 and CO_2 exchange. Oxygenation mainly depends on the extracorporeal blood flow [8], whereas CO_2 transfer mainly depends on the sweep gas flow rate set at the membrane lung (ML) [9, 10].

As described above, high inspiratory O_2 fraction do not correct hypoxemia in the presence of elevated pulmonary shunt. V-V ECMO allows to increase the mixed venous O_2 content, so that the "shunted" blood becomes oxygenated. V-V ECMO is therefore proposed when severe hypoxemia is life-threatening despite low tidal-low volume ventilation, use of moderate to high positive end expiratory pressure (PEEP), continuous neuromuscular blockers infusion and at least one trial of prone positioning [11].

On the other hand, the indication for $ECCO_2R$ deserves more discussion. The more severe is the compromise of the lung function, the higher airway pressure and minute ventilation are required to maintain viable oxygen and carbon dioxide levels. Furthermore, the lung pathological lead to a decrease of the lung compliance, thus requiring higher ventilatory pressures. This high ventilation burden may worsen the lung inflammation (i.e., ventilator induced lung injury, VILI), leading to a vicious circle. Moreover, the simultaneous presence of hypoxic pulmonary vasoconstriction, hypercapnia, and high ventilatory pressures determine an increase pulmonary resistances and pulmonary arterial pressure (i.e., right ventricular afterload), eventually leading to right ventricular dysfunction or failure [12].

The extracorporeal removal of carbon dioxide allow to reduce the ventilatory load down to near-apneic ventilation, which in the experimental model [13] allowed to decreases histologic lung injury and fibroproliferation. Mechanical ventilation during ECMO is discussed in detail in Chap. 31. Briefly, wide variability exists among ECMO centers on how ventilatory setting is modified after the start of extracorporeal gas exchange [14]. In general, tidal volume is usually lowered to 3–6 mL/kg (calculated on ideal body weight) to achieve a plateau pressure below 25 cmH_2O and driving pressure below 12–15 cmH_2O. In addition, to further decrease the ventilation burden, many centers reduce respiratory rate down to 10–15 breaths per minute. Figure 30.1 shows the reduction of ventilation achieved in the first 20 min after the ECMO start in 36 ARDS patients at our center (unpublished data).

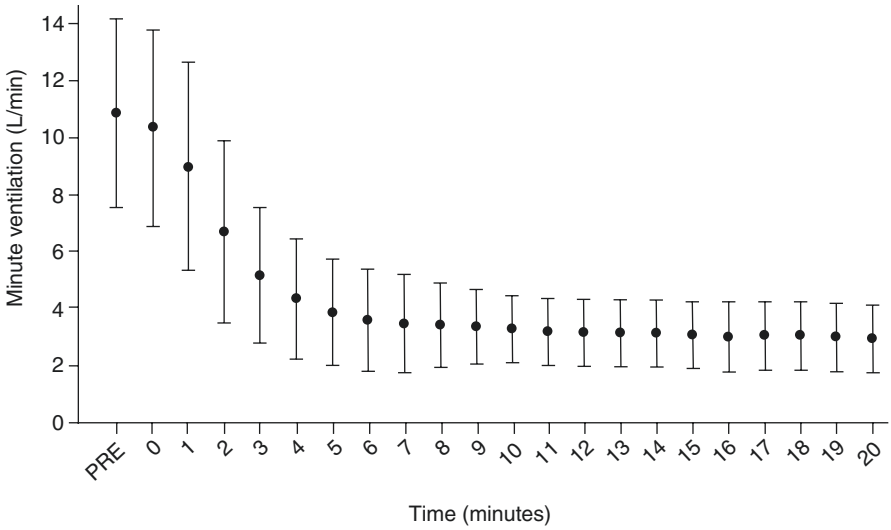

Fig. 30.1 Minute ventilation before and after the ECMO start. Points represent mean values; error bars display standard deviation. *L/min* liters per minute. *$P < 0.05$ vs. step PRE

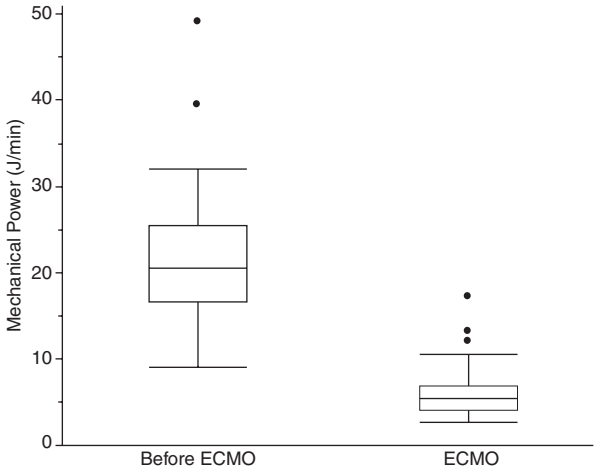

Fig. 30.2 Mechanical power before and after the ECMO start. *ECMO* extracorporeal membrane oxygenation

This reduction of minute ventilation was achieved by reducing the tidal volume from 5.6 ± 1.8 to 4.5 ± 2 mL/kg ($P < 0.001$) and the respiratory rate from 30 ± 5 to 10 ± 2 breaths per minute ($P < 0.001$). The reduction of tidal volume led to a decrease of driving pressure of 4 cmH_2O (from 14 ± 3 to 10 ± 3).

Accordingly, the mechanical power, which represents the amount of total energy transmitted by the ventilator to the damaged lungs, is dramatically reduced after start of ECMO, as shown in Fig. 30.2 (66 ARDS V-V ECMO patients at ASST Monza, unpublished data).

As a common clinical experience, the start of V-V ECMO is followed by a significant improvement of hemodynamics. The normalization of arterial O_2 and CO_2 levels, together with the decrease of intra-thoracic pressures, determines a reduction of pulmonary resistances and right ventricle unloading [15], thus reducing the risk of developing acute cor pulmonale, which is observed in up to 22% of severe ARDS patients and is strongly associated with mortality [16].

30.3 "Full" V-V ECMO Versus Low-Flow $ECCO_2R$

Typically, in very severe ARDS patients requiring extracorporeal gas exchange high-flow veno-venous ECMO is the technique of choice. Severe hypoxemia defined by PaO_2/FiO_2 below 50–80 mmHg (at 100% FiO_2) and severe respiratory acidosis (pH <7.25) are the main inclusion criteria used in clinical trials on extracorporeal support [2, 17–19]. However, Gattinoni et al. challenged the idea that a very low arterial oxygen tension determines tissue hypoxia, and postulated that almost all severe ARDS patient might be managed with low-flow systems. Indeed, patients with an arterial O_2 tension lower than 60 mmHg do not seem to suffer from any organ damage [10]. Actually, the greatest benefit of ECMO in the EOLIA trial [17] was found in the group of patients who presented with a degree of respiratory acidosis which prevented protective ventilation (24% mortality in the ECMO group vs. 55% in the control group). This finding may suggest that the benefit from ECMO probably relies more on VILI prevention than on the improvement of arterial O_2.

When the extracorporeal gas exchange is only required to decrease the mechanical ventilation load, a less invasive $ECCO_2R$ technique may be a reasonable option. However, defining a ventilatory burden cutoff which mandates the extracorporeal CO_2 removal may prove challenging. Actually, a recent trial on $ECCO_2R$ and ultraprotective lung ventilation—the Supernova study [20]—, used an oxygenation index and not ventilatory load as an inclusion criterion. This study only reported a slight decrease of plateau pressure using low or intermediate blood flow by two different devices.

The $ECCO_2R$ system (cannula size, pump and membrane surface) limits the maximum blood flow achievable, becoming useless in case of life-threatening hypoxemia. Ultraprotective ventilatory strategies (i.e., tidal volume reduction below 6 mL/kg) aim at VILI reduction in critical ARDS patients. However, this often results in lung de-recruitment and consequently in a worsening of hypoxia [21].

Indeed, in a study of $ECCO_2R$ safety, prone positioning and conversion to high-flow V-V ECMO were required as rescue therapies for life-threating hypoxemia in 2 and 4 out of 15 patients, respectively [22]. Besides, due to modulation of the respiratory quotient by the membrane lung, $ECCO_2R$ could expose patients to paradoxical hypoxemia [23, 24].

In the past, our group has proposed and validated a mathematical model of oxygenation during V-V ECMO [8], with a high accuracy and predictive power. Through this model, we retrospectively analyzed data of 76 patients treated with high-flow V-V ECMO at our institution. Among these patients, a blood flow reduction down

to the $ECCO_2R$ range (i.e., 1 L/min) would have determined a severe desaturation (i.e., a peripheral oxygen saturation below 85%) in 30 patients (39%), despite 100% of O_2 inspiratory fraction at the ventilator [unpublished data]. Due to the retrospective, preliminary and in silico nature of these data, further research is warranted to determine the safety and feasibility of a pure $ECCO_2R$ technique versus a high-flow V-V ECMO in severe ARDS patients.

As explained above, an extracorporeal blood flow of 500–1500 mL/min is required to remove a significant fraction of the total CO_2 production (VCO_2). Experimental techniques were developed to improve the extracorporeal CO_2 extraction of the membrane lung, with the aim of extracting up to half of VCO_2 from a very low blood flow, such as the one used for renal replacement techniques (150–300 mL/min). This would allow to use small dual-lumen catheters (e.g., 12–14 French) and, hypothetically, regional citrate anticoagulation.

Blood acidification has been proposed as an experimental technique to increase the carbon dioxide removal capability of the membrane lung [25]. Acidification converts bicarbonates into carbon dioxide, increasing the carbon dioxide transfer [26, 27]. More recently, respiratory electrodialysis has been described as a new experimental technique to efficiently performs $ECCO_2R$ [28, 29]. When compared to conventional $ECCO_2R$, respiratory electrodialysis almost doubled the ML CO_2 removal and halved minute ventilation. Due to the very preliminary nature of these experimental findings, further research is warranted in this field.

30.4 Evidence for Extracorporeal Gas Exchange in ARDS Patients

As mentioned, V-V ECMO is an indisputable life-saving therapy for refractory hypoxemia and a strong physiological rationale supports its use when high plateau pressures and/or tidal volumes are required. However, it is unclear how to define the oxygenation and ventilation load cutoffs which mandates the start of the V-V extracorporeal support.

Recently, two important studies have changed the evidence on V-V ECMO use.

About 10 years ago, the CESAR trial [18] clearly showed that the most severe ARDS patients should be transferred to an ECMO-capable center to significantly improve survival without severe disability. Even if only 75% of the patients received ECMO, it's highly likely that the use of ECMO had an impact on the survival benefit.

The more recent EOLIA trial [17] randomly assigned 249 patients with severe ARDS to receive early V-V ECMO or conventional tidal volume (Vt) and pressure limited ventilation (including late ECMO as rescue therapy). Despite inconclusive survival results (35% and 46% mortality in ECMO and control group, respectively, $P = 0.09$), the high percentage of sicker patients that crossed over from the conventional treatment group to the ECMO group for rescue therapy (28%) endorsed the use of V-V ECMO in life-threatening hypoxemia. Moreover, per-protocol and Bayesian post hoc analysis provided more favorable interpretation of the study

results [30, 31]. Thus, an individual patient data meta-analysis [30] of EOLIA and CESAR trials found a significant decrease in 90-day mortality in patients supported by ECMO compared with conventional management.

The combined use of $ECCO_2R$ and mechanical ventilation has proved to be feasible when compared to mechanical ventilation (MV) alone [7, 20, 22]. However, the benefit of $ECCO_2R$ need to counterbalance the risks of the technique. The recently published REST trial [21] aimed to establish whether $ECCO_2R$ and ultraprotective ventilation may improve all-cause mortality in comparison with standard of care. The study was stopped prematurely due to futility and feasibility issues. Ninety-day mortality rate was 41.5% in the experimental group (lower tidal volume ventilation + $ECCO_2R$) vs. 39.5% in the standard care group ($P = 0.68$). However, there were fewer ventilator-free days and more serious adverse events in the extracorporeal carbon dioxide removal group. Adverse events in the extracorporeal carbon dioxide removal group included intracranial hemorrage, which occurred in 9 patients (4.5% vs. 0% in the control group), and bleeding at other sites (3.0% vs. 0.5%). The study had some relevant limitations, including that the tidal volume target (3 mL/kg) in the experimental arm was not achieved. However, based on these findings, $ECCO_2R$ cannot yet be recommended as a strategy to improve ARDS patients' outcome.

30.5 Outcome of ARDS Patients Treated with V-V ECMO

The Extracorporeal Life Support Organization (ELSO) collects and publishes on a regular basis the number of ECMO runs and their outcome. Overall, the reported hospital survival rate of adult patients treated with V-V ECMO is 59% [32]. Over the last 10 years, the number of ECMO runs has almost tripled [32], and the recent SARS-CoV-2 pandemic led to a further rise of V-V ECMO use worldwide. After early reports from China of very high mortality rates of COVID-19 patients treated with ECMO [33], large observational studies showed satisfactory outcomes in this population. A large observational study from the Extracorporeal Life Support Organization (ELSO) registry [34] included 1035 COVID-19 patients and reported a 90-day mortality of 37%. Later reports [35–37] which included patients from the second COVID wave in fall 2020 showed a trend toward increased mortality (48–60%). This finding was only partly explained by patient characteristics at baseline. The authors hypothesize that failure of prolonged noninvasive ventilation strategies before intubation and increased lung damage may have influenced this worse outcome [36]. This underlines how, in the context of acute respiratory distress, V-V ECMO should only be considered as a bridge-to-recovery therapy, and should not be indicated when lung damage is deemed irreversible.

30.6 Should the Number of ECMO Centers Be Increased?

In the last decade the number of ECMO centers has increased steadily [32]. It might be tempting to think that every hospital/ICU should develop the ECMO capability, to be able to face any severe respiratory (or cardiac) failure refractory to

conventional therapies. However, providing ECMO requires a multidisciplinary team (i.e., physicians, nurses, perfusionists) with specific skills that are difficult to develop in a short time and require a high case volume to be maintained. Several studies showed that a major determinant of the outcome of ECMO patients is the center case volume [38, 39]. For this reason, a hub and spoke model seems able to provide the best result s [39]. 24/7 mobile ECMO teams are available in many ECMO centers and allow a safe patient retrieval with good outcomes. The CESAR trial [18] showed unequivocally that centralization of patients with severe but potentially reversible respiratory failure to an ECMO-capable center significantly improves survival. Peripheral "spoke" hospital must develop the delicate skill of early identification and management of ARDS patients at risk at deterioration and should consult ECMO centers timely, as prolonged mechanical ventilation (especially if not protective) has proved to be an independent predictor of poor outcome [39].

30.7 Conclusions

In a nutshell, V-V ECMO provides oxygenation and allow a more protective ventilation strategy [14, 40]. Considering its strong rationale and the results of recent randomized trials [30], its application in experienced ECMO centers should be considered for the most severe ARDS patients when other therapies (i.e., prone positioning) fail. However, defining the appropriate level of lung rest, the setting of mechanical ventilation and the role of assisted breathing during extracorporeal support still need further investigation.

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Mechanical Ventilation Setting During ECMO

31

Luigi Camporota and Eddy Fan

31.1 Introduction

31.1.1 Mechanical Ventilation Strategy in ARDS

In patients with acute respiratory distress syndrome (ARDS), mechanical ventilation is instituted to support gas exchange and the work of breathing, while the patient receives treatment from the underlying disease. It is now clear, however that the mechanical forces generated by the ventilator can damage the small and inhomogeneous diseased lung through pathophysiological mechanisms known as

L. Camporota (✉)
Department of Adult Critical Care, Guy's and St Thomas' NHS Foundation Trust, King's Health Partners, London, UK

Division of Centre of Human Applied Physiological Sciences, King's College London, London, UK

St Thomas' Hospital, London, UK
e-mail: luigi.camporota@gstt.nhs.uk

E. Fan
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Medicine, University of Toronto, Toronto, ON, Canada

Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

Division of Respirology, Department of Medicine, University Health Network, Toronto, ON, Canada

Toronto General Hospital Research Institute, Toronto, ON, Canada
e-mail: eddy.fan@uhn.ca

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ventilator-induced lung injury (VILI). These mechanisms are also the factors that contribute to the development of extra pulmonary organ failure [1, 2].

Based on the appreciation of VILI, over the last 50 years the aim of mechanical ventilation has gradually shifted from focussing on achieving near-normal arterial oxygen and carbon dioxide tension (PaO_2 and $PaCO_2$) levels regardless of the cost in terms of airway pressures and tidal volumes, to the goal of minimising the intensity of mechanical energy delivered to the lungs (mechanical power). In this context, particular attention is now placed to the setting of a respiratory rate as low as possible (based on $PaCO_2$) [3], the use of moderate positive end-expiratory pressure (PEEP) with the avoidance of routine use of recruitment manoeuvres (RM) [2, 4], and tidal volumes which are in proportion to the resting lung volume. This latter concept is reflected in the measure of driving pressure, which represents the ratio between tidal volume delivered and compliance of the respiratory system [5].

31.1.2 Mechanical Ventilation Strategy in Severe ARDS Receiving ECMO

The association between the different components of the mechanical power [6] and outcome is even more relevant for patients with very severe ARDS who receive extracorporeal membrane oxygenation (ECMO) [1], given that the very low lung volume and greater heterogeneity makes the lung parenchyma more vulnerable to mechanical stress and strain—and therefore VILI.

Several studies have also demonstrated the value of a lung protective ventilation and ECMO in patients with ARDS [7]. The evidence available so far seems to show that ventilating patients with lower driving pressure (tidal volumes) and respiratory rate once on ECMO is feasible [8–12] and leads to improved outcomes [13, 14].

In this chapter, we will review some of the evidence related to mechanical ventilation during ECMO and some practical recommendations.

31.1.3 Effects of ECMO on Gas Exchange and Interactions with Native Lung Function

Venovenous ("respiratory") ECMO allows deoxygenated blood drained from a central vein to be reinfused—fully oxygenated and decarboxylated—into the vena cava or the right atrium at sufficient flows (3–7 L/min) to achieve oxygen delivery able to satisfy metabolic demands.

In patients with ARDS not on ECMO, the arterial oxygen content (CaO_2) depends on the shunt fraction of the native lung, and on the oxygen content of the mixed venous blood:

$$CaO_2 = CcO_2 \times \left(1 - \frac{Q_s}{Q_t}\right) + \left(CvO_2 \times \frac{Q_s}{Q_t}\right) \quad (31.1)$$

where, $1 - (Q_s/Q_t)$ is the portion of the cardiac output going through the ventilated lung parenchyma, and Q_s/Q_t is the portion of the cardiac output perfusing non-ventilated lung areas.

In patients fully dependent on ECMO (i.e. with no residual native lung function) the CaO_2—in its simplest form, without accounting for recirculation (see below)—is:

$$CaO_2 = C_{post-oxy}O_2 \times ECBF + CvO_2 \times (CO - ECBF) \tag{31.2}$$

This formula is analogous to Eq. (31.1) where ECMO blood flow is noted as ECBF and CO is the cardiac output of the patient, CvO_2 is the content of oxygen in the venous blood and $C_{post\text{-}oxy}O_2$ content of the blood exiting the oxygenator.

By rearranging Eq. (31.2):

$$CaO_2 = \left(\frac{ECBF}{CO}\right) \times C_{post-oxy}O_2 + \left[1 - \left(\frac{ECBF}{CO}\right)\right] \times CvO_2 \tag{31.3}$$

Using this formula, the oxygen content is expressed in terms of the ratio between the ECBF and the cardiac output—in a similar way as the shunt equation of the native lung.

It becomes clear that oxygen content depends not only on the ECMO blood flow and the content of oxygen in the venous blood, but also on the ratio between ECBF and the patient's cardiac output. To understand this concept, we have to consider how the venous return, equal to the patient cardiac output, is "split" into two components: (1) one part—equal to the ECBF—will pass through the oxygenator and therefore will return to the right atrium fully saturated with oxygen ($S_{post\text{-}oxy} = 100\%$; $P_{post\text{-}oxy}O_2 \sim 60–70$ kPa or 450–525 mmHg); (2) the second part of the venous return—which is equal to the amount of flow that exceeds the ECBF (i.e. CO − ECBF) will have the saturation of the venous blood. Therefore, the mixed venous blood of the patient (the oxygenation of the blood in the pulmonary artery) will be a mixed "weighed average" of the two in a proportion that will depend on: the ratio between ECBF and CO; the venous oxygenation and the functioning of the membrane (i.e. the ability to fully oxygenate the venous blood).

31.1.4 Interaction Between the Native and the Artificial Lung

Form the principles discussed above, is clear that unless the ECBF is exactly equal (or greater—if we consider recirculation) than the cardiac output, the patient arterial saturation will be less than 100%, and often in the range of 85–92%. In this context, the management of the native lung through appropriate ventilation can be relevant to maintain a certain degree of native lung function. So, it is relevant to reflect that once a patient is placed on ECMO, the native lung function may deteriorate because of two main physiological phenomena:

1. Abolition of hypoxic vasoconstriction—(from hyper-oxygenation of the mixed venous blood) with an increase in the physiological shunt of the native lung,
2. Reduction in alveolar oxygen tension resulting from the CO_2 removed by the membrane lung—and a reduction of the alveolar CO_2 (demonstrated by the reduction in the end tidal CO_2). The reduction of the alveolar CO_2 is responsible for the reduction in the respiratory quotient of the natural lung and a progressive fall in the alveolar PO_2 based on the alveolar gas equation:

$$PAO_2 = \left[FiO_2 - P_{atm-H_2O} \right] - \left(\frac{PaCO_2 \times VO_2}{VCO_{2NL}} \right) \quad (31.4)$$

Where VO_2 is the oxygen consumption and VCO_{2NL} is the amount of CO_2 removed by the native lung per minute. It is important to note that an ultra-protective strategy of ventilation (severe hypoventilation with normocapnia) can lead to reabsorption atelectasis, and a reduction in inspiratory pressure can cause significant reduction in end-expiratory lung volume, and lung collapse due to compression atelectasis. All these conditions are avoidable using an adequate level of PEEP.

Along with the hemodynamic changes which follow ECMO initiation, these physiological mechanisms and changes in ventilator settings contribute to an increase in shunt fraction and a worsening in the gas exchange of the native lung (Fig. 31.1).

31.1.5 Mechanical Ventilation on ECMO: General Principles

The settings used to ventilate patients with severe ARDS on ECMO are highly variable across different international ECMO centres, and there no universally accepted consensus on the optimal strategy. Although the majority of the centres reports adopting a "lung rest" strategy with low tidal volumes [15], there is large variation in terms of PEEP setting and titration and use of recruitment manoeuvres [16] and less than one-third of centres have an explicit mechanical ventilation protocol for ECMO patients [16]. This variation in practice reflects the lack of robust evidence from randomised trials (RCT) on one hand, and the variation in background, expertise, and case-mix within each ECMO centre on the other.

However, it appears logical that the primary focus of mechanical ventilation during ECMO should be that of averting VILI, while promoting lung rest and healing [7]. Therefore, mechanical ventilation should maximise lung protection, while gas exchange is supported by ECMO.

The "standard" ventilation settings used in the CESAR study [17] were the following: FiO_2 reduced to 0.3 (or the lowest possible); tidal volume of 2–4 mL/kg of predicted body weight to limit the plateau pressure to 20–25 cmH_2O; PEEP—initially maintained to defend mean airway pressure then gradually reduced to 10 cmH_2O, giving a driving pressure of 10 cmH_2O. Respiratory rate was maintained

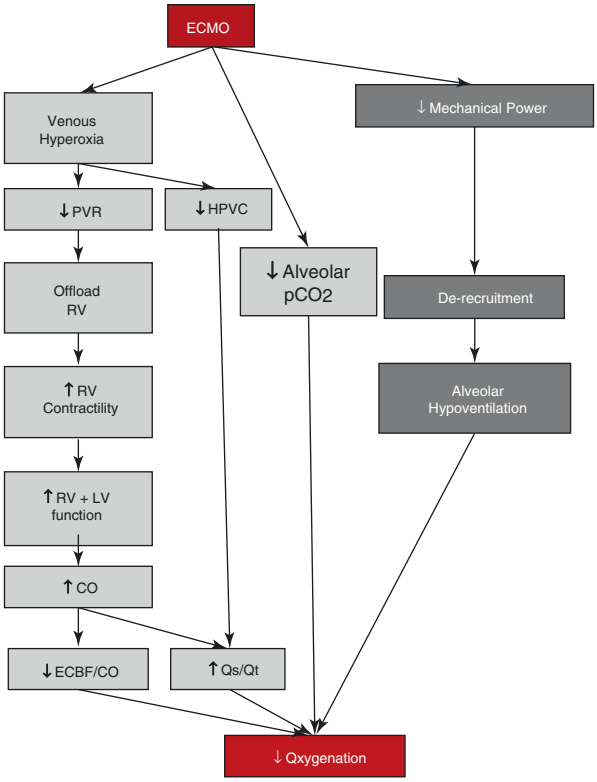

Fig. 31.1 Pathophysiological changes that may affect arterial oxygenation after ECMO initiation. VV-ECMO increases venous oxygenation and allows a reduction of mechanical power. ECMO produces venous hyperoxia which in turn reduces pulmonary vascular resistance and hypoxic pulmonary vasoconstriction. This improves right ventricular function, cardiac output and increase shunt (Q_s/Q_t). The cardiac output (CO) improves and reduce the ration between extracorporeal blood flow (ECBF) and cardiac output. All these changes can result in a lower arterial oxygen tension

at 10 breaths/min. A similar strategy was used in the more recent EOLIA trial [18], but the respiratory rate was permitted to range between 10 and 30 breaths/min.

Although data from RCTs are more limited in patients supported by ECMO, the evidence in the management of ARDS accumulated over the last 20 years can offer some guiding principles that can be safely extrapolated to patients on ECMO.

If we consider the single guiding principle that the determinant of VILI—by definition—is the total energy delivered to the lung by the ventilator (in the case of controlled ventilation), it is clear that the best way to reduce VILI is to minimise each individual components of the mechanical power equation: respiratory rate, driving pressure (through tidal volume), inspiratory flow, and PEEP [6, 19] (Fig. 31.2).

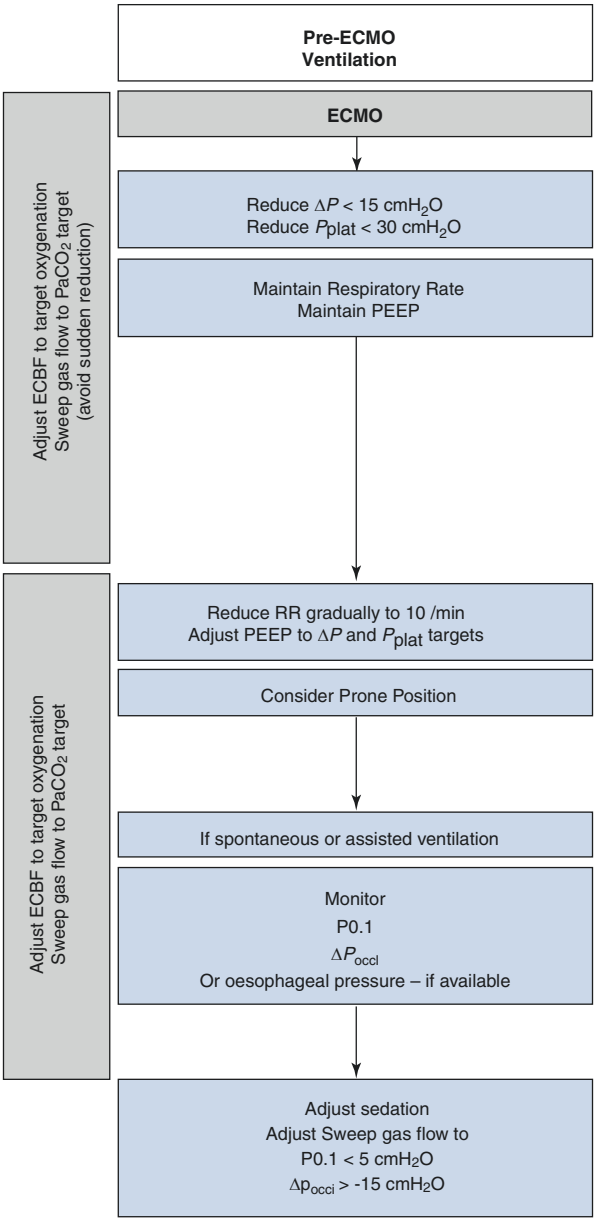

Fig. 31.2 Mechanical ventilation during ECMO: steps and targets

31.1.6 Mechanical Ventilation Setting on ECMO

31.1.6.1 Tidal Volume

Although there is still debate on what is the optimal tidal volume (V_T) referenced to predicted body weight (6 vs. 4 vs. 3 mL/kg), there is growing evidence supported by strong physiological principles that the determinant of volutrauma is lung *strain*—measured as the ratio between tidal volume and the resting lung volume (functional residual capacity—FRC).

In the absence of bedside measures of FRC, the relationship between FRC (the volume of the lung that can be ventilated, or "baby lung") and compliance of the respiratory system (C_{RS}) can be used to make approximation on the level of strain (Eq. 31.5) and therefore make clinical decisions regarding setting the most appropriate tidal volume whether V_T is appropriate for the size of FRC.

$$\text{Strain} = \frac{V_T}{\text{FRC}};\ \text{FRC} \propto C_{RS} \rightarrow \text{Strain} \approx \frac{V_T}{C_{RS}} \tag{31.5}$$

$$\text{Strain} = \frac{V_T}{\dfrac{V_T}{P_{plateau} - \text{PEEP}}} = P_{plateau} - \text{PEEP} \tag{31.6}$$

Indeed, if FRC is substituted for C_{RS} in the strain equation (Eqs. 31.5 and 31.6), one can see how driving pressure (plateau pressure minus PEEP) represents lung strain. Therefore, driving pressure can be used to set tidal volume regardless of the severity of ARDS [3, 20]. ECMO makes it possible to reduce driving pressure below the threshold of 14 cmH_2O, beyond which the risk of mortality increases [3, 5].

A multicentre, prospective cohort study of patients undergoing ECMO for ARDS during a 1-year period in 23 international ICUs showed that after ECMO initiation V_T was decreased from 6.4 ± 2.0 to 3.7 ± 2.0 mL/kg PBW, reducing the driving pressure from 20 ± 7 to 14 ± 4 cmH_2O and—with a simultaneous reduction in respiratory rate—mechanical power was markedly reduced from 26.1 ± 12.7 to 6.6 ± 4.8 J/min [8]. Similar reductions were achieved in the EOLIA trial [18] and in a multicentre observational study [11]. A reduction in tidal volume and driving pressure is strongly associated with mortality in ECMO patients, with a 6% increase in the risk of in-hospital mortality for each additional cmH_2O of driving pressure (hazard ratio 1.06; 95% CI 1.03–1.1) [12].

31.1.6.2 Respiratory Rate

Respiratory rate is probably the most underappreciated determinant of VILI. In patients with ARDS not on ECMO, respiratory rate is often increased to compensate for the low tidal volumes and control hypercapnia. The removal of CO_2 via the membrane lung allows the reduction in respiratory rate even to very low levels. This strategy can decrease inflammation and lung injury [21, 22]. Based on currently available data, it is recommended that respiratory rate on ECMO is set as low as possible—using the CESAR protocol [17] ta 10/min, or in the range of 4–15/min as recommended by ELSO [23].

31.1.6.3 PEEP

Recommendations regarding PEEP setting during ECMO are more variable and may depend on lung recruitability and mean airway pressure pre-ECMO [24]. While very low PEEP levels may cause progressive de-recruitment, atelectasis formation and progressive lung consolidation and fibrosis, very high PEEP levels can contribute to static volutrauma, increased lung stress and strain, haemodynamic compromise and ECMO cannula access insufficiency. Therefore, PEEP levels between 10 and 15 cmH_2O are a reasonable compromise, provided that plateau pressure and driving pressure remain within safe ranges.

31.1.7 Additional Considerations

31.1.7.1 Prone Position

The use of prone position in ECMO is possible and observational data suggests it is associated with an improvement in outcome [25, 26]—although it may be associated with longer ECMO duration [26]. While definitive evidence is awaited, prone position in ECMO seems a useful additional strategy to protect the lung and minimise de-recruitment post-ECMO. Important precautions need to be considered to avoid pressure areas or occlusion/kinking of cannulae which will interfere and interrupt extracorporeal blood flow.

31.1.7.2 Respiratory Effort

One potentially problematic issue related to the ventilation of patients on ECMO is the transition between mandatory ventilation and spontaneous/assisted ventilation. Patients on ECMO may have high respiratory drive and inspiratory effort despite a relatively normal gas exchange mainly due to the high elastance which stimulates respiratory drive and effort, leading to hunger and distress. These symptoms may not be improved by tracheostomy, particularly during the early stages of the disease [27], and may be associated with complications if the patients is fully ECMO dependent or coagulopathic [28]. The increased respiratory effort can cause large increases in pleural pressure, resulting in an uncontrolled increase in local transpulmonary pressure, with lung injury and barotrauma—a process named patient self-inflicted lung injury (P-SILI) [29].

Clinicians should be aware of this possibility and monitor inspiratory efforts using measures such as P0.1, occlusion pressure (P_{occ}) [30] or using more invasive methods such as oesophageal pressure or the electrical activity of the diaphragm (Eadi). An occlusion pressure can be easily performed using and end-expiratory hold manoeuvre. The occlusion pressure is the difference between PEEP and the most negative airway pressure deflection during the first breathe after the occlusion. Ideally, patients should be managed so that they can maintain a P0.1 < 4–5 cmH_2O and an occlusion pressure >−15 cmH_2O [31].

31.2 Conclusion

The general principle of ventilation during ECMO is to maximise lung protection while gas exchange is maintained through the extracorporeal membrane lung. Careful attention and monitoring of driving pressures, respiratory rate and PEEP selection is essential during mandatory ventilation, while monitoring of respiratory effort and drive can reduce the risk of patient self-inflicted lung injury.

Declaration of Interests The authors declare that they have no conflict of interests.

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Part IV

Monitoring of Mechanical Ventilation

Ultrasound Assessment of the Respiratory System

32

Mark E. Haaksma, Marry R. Smit, and Pieter R. Tuinman

32.1 Introduction

Point-of-Care Ultrasonography is an invaluable diagnostic- and monitoring tool for intensivists that allows for rapid assessment of the entire respiratory system [1]. With thorough practice and good knowledge of anatomy and understanding of ultrasonographic patterns, vast amounts of information can be obtained at the bedside at negligible patient burden and cost. As such, its routine use in daily clinical practice is highly recommended. In ventilated patients, pulmonary disease is often the cause or consequence of mechanical ventilation and as such must be quickly detected and treated. In the following chapter, we discuss key concepts of lung-, diaphragm- and accessory respiratory muscle ultrasonography and its potential application in the critical care setting.

M. E. Haaksma (✉) · P. R. Tuinman
Department of Intensive Care Medicine, Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands

Amsterdam Leiden Intensive Care Focused Echography (ALIFE), Amsterdam, The Netherlands

Amsterdam Cardiovascular Sciences Research Institute, Amsterdam UMC, Amsterdam, The Netherlands
e-mail: m.haaksma@amsterdamumc.nl; p.tuinman@amsterdamumc.nl; https://www.alifeofpocus.com; https://www.alifeofpocus.com

M. R. Smit
Department of Intensive Care Medicine, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands
e-mail: m.r.smit@amsterdamumc.nl

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32.2 The Lungs

32.2.1 Introduction

The following section and Fig. 32.1 will briefly explain the most common findings in lung ultrasound and its application in clinical practice.

32.2.1.1 Pleura

The pleura indicates the interface between the chest wall tissue (fluid-rich) and the lung (air-rich). The parietal- and visceral pleura can't be distinguished from another and appear as a single, horizontal, hyperechogenic line. During the respiratory cycle, they create a glistening appearance called lung sliding. Absence of lung sliding is always pathological and can indicate a variety of pathology, e.g., pneumothorax, unilateral intubation or consolidation. M-mode can be a helpful tool if the

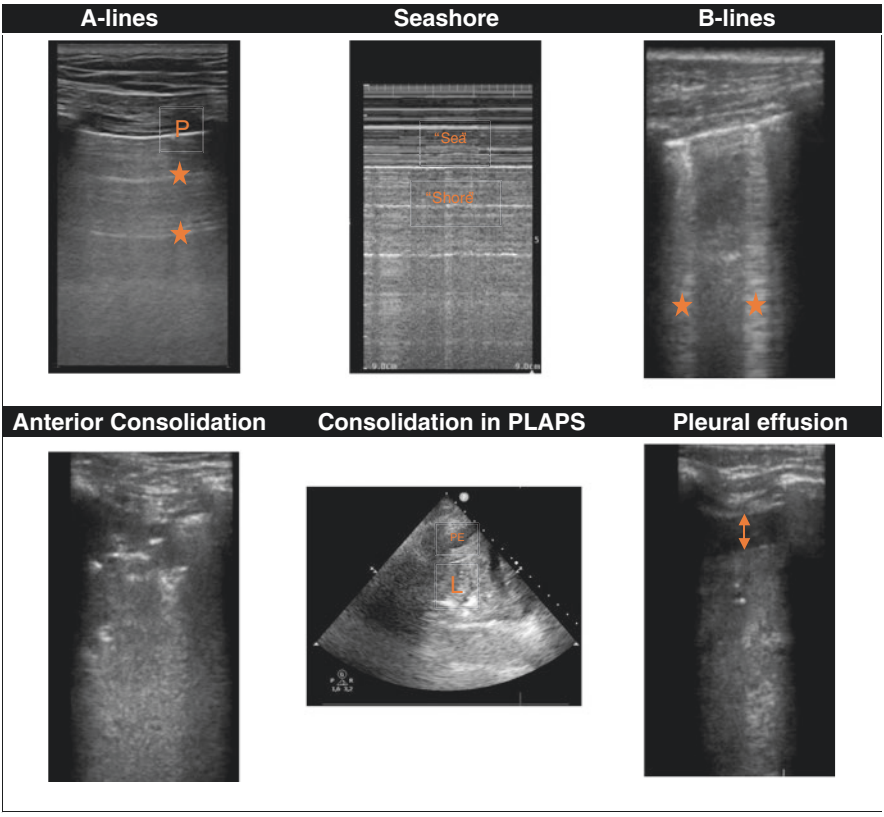

Fig. 32.1 Artefacts and signs observed during lung ultrasound. *P* Pleura, *PE* pleural effusion, *L* lung, *Star* B-line, *Arrow* pleural effusion

clinician is unsure if lung sliding is present, which can reveal the seashore sign (lung sliding present) or the barcode sign (lung sliding absent).

32.2.1.2 A-Lines

A-lines are horizontal reverberations artifacts, created by ultrasound waves reflected between the transducer and pleura. Their presence indicates a high difference in acoustic impedance, between soft-tissue and air. As such, their presence indicates air below the pleura, being aerated lung tissue or pneumothorax.

32.2.1.3 B-Lines

B-lines are vertical comet-tail artifacts, arising as consequence of thickened interlobular septae. This can be a consequence of fluid extravasation and thus an altered ratio between air and fluid, for example due to inflammatory processes or increased hydrostatic pressure. The presence of 1–2 B-lines is deemed physiological and only if more than two B-lines are present within a single intercostal space pathology is assumed, the so-called interstitial syndrome. On the ICU, the most frequent causes of bilateral interstitial syndrome are cardiogenic pulmonary edema or ARDS, whereas for unilateral cases, pneumonia is the most likely explanation.

32.2.1.4 Consolidation

If lung parts completely lose aeration, ultrasound waves readily traverse the lung parenchyma and generate an anatomical image that appears tissue like/consolidated. Non-artifactual images of lung tissue are always pathological and can for example be seen in atelectasis, pneumonia or ARDS. In the anterior lung regions this can either be seen as "shred sign" (derived from the morphological appearance of a shredded pleura) or as entire consolidation (most often observed in the dorso-caudal lung regions).

32.2.1.5 Pleural Effusion

Pleural effusion can be seen as a hypoechogenic layer between the visceral and parietal pleura. Typically, its thickness changes with the respiratory cycle, so-called sinusoid sign, and follows distribution according to gravity.

32.2.2 Application in Clinical Practice

Ultrasonographic evaluation of the lung is a still evolving discipline and, as such, heterogeneity exists across several aspects when applied in clinical practice. While it is important to be aware of these and we list these below, it should be noted that, generally speaking there is no machine, probe or technique that is clearly superior to others in every aspect. As such, these differences are accepted and personal preference of the physician plays an important role.

Starting with the ultrasound machine, even the most basic versions will normally suffice and might sometimes even be superior due to their lack of artifact erasing and other filtering software. Regardless of type or age, carefully checking whether

deactivating artifact erasing software is possible or a special "lung-setting" exists, is important. Choice of transducer is dependent on the preference of the physician and target of visualization, with higher frequency transducers allowing for more accurate detection of pleural pathology while lower frequency transducers provide better overview. Their placement varies according to the protocol performed (discussed later) but should generally be placed perpendicular to the lung surface and squarely across the intercostal space. Further specifications of image depth and gain are still a subject of discussion, but it is generally recommended to use a depth of at least several centimeters to fully appreciate the extent of the reverberation artifacts such as A- and B-lines.

32.2.2.1 Diagnosis of Acute Respiratory Failure

The "BLUE"-protocol (Fig. 32.2) was developed to identify the most common causes of acute respiratory failure [2]. To this end, ultrasonographic signs and artifacts observed during pulmonary ultrasound potentially combined with scanning for deep venous thrombosis, are used to diagnose common causes of acute respiratory failure. Briefly summarized, three points per hemithorax are scanned (two anterior and one posterior point). The anterior points are evaluated based on lung sliding and the predominant ultrasonographic patterns to assign a profile:

- A or A′-profile: A-line predominance (A′: in the absence of lung sliding).
- B or B′-profile: B-line predominance (B′: in the absence of lung sliding).
- A/B-profile: unilateral A-lines and contralateral B-lines.
- C-profile: tissue-like pattern in any anterior point.

The posterior point is only denoted as being present (e.g., pulmonary effusion, consolidated lung tissue) or absent (unaffected lung moving through the image).

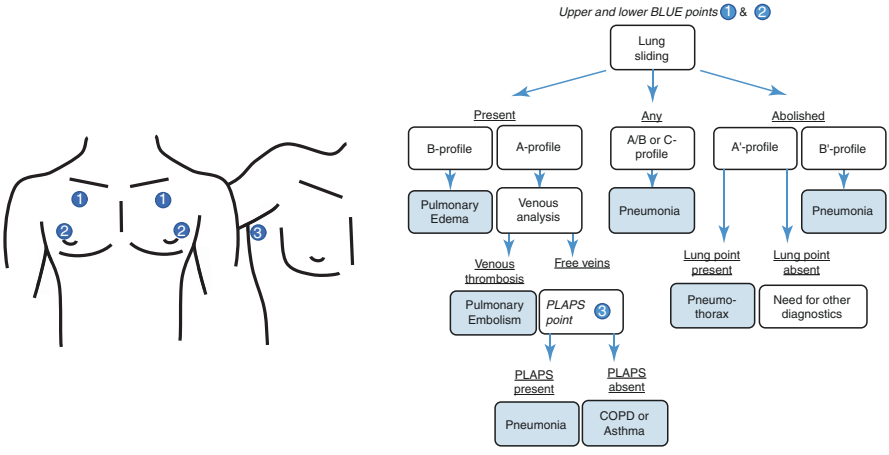

Fig. 32.2 The BLUE-protocol. Left: Anterior BLUE-points (1 and 2) and PLAPS-point (3). Right: BLUE-protocol flow chart

From this step, depending on the previous steps, either a diagnosis can be established following a hierarchical decision tree or analysis for deep venous thrombosis is necessary. The endpoints of the decision tree are: pneumonia, pneumothorax, pulmonary embolism, pulmonary edema and chronic obstructive pulmonary disease/asthma.

It should be noted, that this is a simplified explanation of the protocol and for a more detailed description the readers are referred to the original paper [2]. In addition, the protocol was developed in an emergency room (hence encompassing the most prevalent diseases in this setting) and not for ICU patients. Nevertheless, this should not discourage its use as it can offer important insights, also in ventilated patients. Potential additions and alterations to the protocol with other signs and tools such as color Doppler imaging, airbronchograms and pleural abnormalities have been suggested and interesting future steps but beyond the scope of this chapter [3].

32.2.2.2 Monitoring Lung Aeration

Loss of lung aeration leading to impaired gas exchange is a common occurrence in mechanically ventilated patients. The causes are numerous and range across, among others, mechanical-, infectious- and hydrostatic origins. Its detection, treatment and monitoring are an important part of everyday clinical practice and all three aspects can be readily achieved with ultrasound. It entails scanning 12 lung regions and calculation of a total Lung Ultrasound Score (LUS) based on the pattern observed per point assessed. The following patterns can be observed (Fig. 32.3):

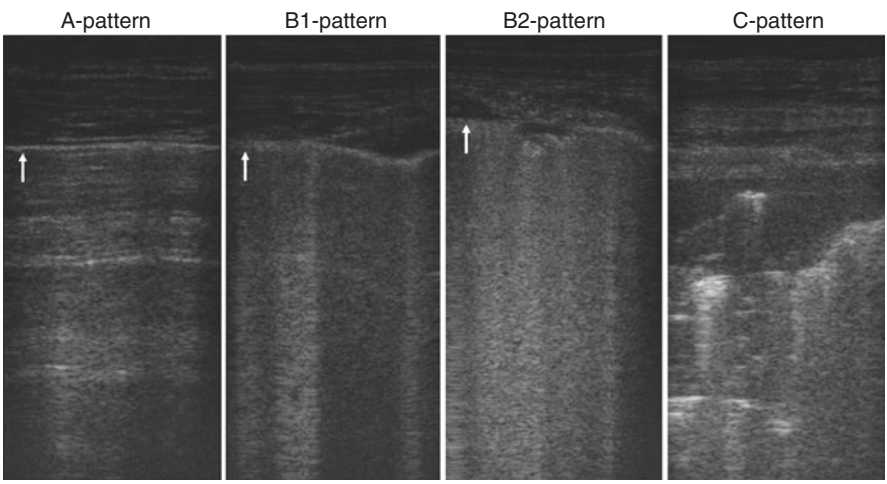

Fig. 32.3 Lung ultrasound score patterns. White arrows indicate the pleura in the ultrasound images

- A-pattern (only A-lines) = 0.
- B1-pattern (B-lines, ≥3 well-spaced) = 1.
- B2-pattern (B-lines, ≥3 coalescent) = 2.
- C-pattern (Consolidated lung tissue) = 3.

The LUS is then calculated as the sum of all scores per region scanned and ranges from 0 to 36. Studies have shown a good correlation of the score with chest CT and has therefore been proposed as feasible, less invasive and more cost-effective alternative [4–6]. This approach can also be used to guide fluid management in ICU, with studies showing a reduction of total fluid balance with regular ultrasound use [7]. Studies evaluating a standardized approach and its effect on clinical outcomes are currently being performed.

32.2.2.3 Lung Ultrasound-Guided Mechanical Ventilation

Regular assessment of lung aeration as described above can also be used to guide ventilator settings [8]. Generally speaking, patients with a diffuse distribution of aeration loss, i.e., also anterior lung fields, can be viewed as PEEP responders. Those with focal loss of aeration, which is typically seen as dorsolateral consolidation with unaffected anterior fields, are more likely to experience detrimental effects of additional PEEP through overdistension of the lungs [8]. Both groups might benefit from prone positioning.

32.2.2.4 Detection and Draining Pleural Effusion

Pleural effusions can be easily detected and quantified with ultrasound. To this end, several approaches exist, however, none having been proven to be superior to the others [9, 10]. The simplest approach is measuring the maximum distance between visceral- and parietal pleura, with the patient in supine position, at maximum inspiration with the transducer placed dorso-laterally. The measured value in millimeters is then multiplied by 20 to yield the volume of the effusion in milliliters (Pleural effusion volume (milliliter) = measured distance (millimeter) × 20).

While it is hypothesized that typifying pleural effusion through ultrasound is possible, with transudates appearing hypoechogenic and homogeneous while exudates appearing echogenic and heterogeneous, recent evidence implies that this is often not the case [11]. As such, assessing the origin of the effusion based on ultrasound, should be attempted carefully and ideally together with other clinical parameters.

32.3 Diaphragm

32.3.1 Introduction

Under physiological circumstances, the diaphragm is the main respiratory muscle. Its contraction results in its shortening, thickening and caudal displacement. These changes can be readily visualized through ultrasonography (Fig. 32.4) and can be

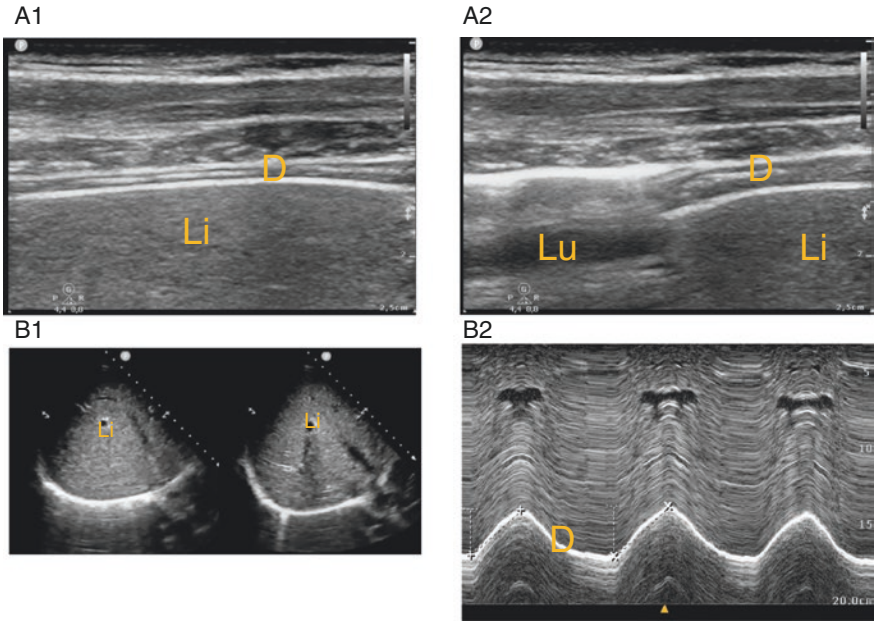

Fig. 32.4 Diaphragm ultrasound. (**a1**) Diaphragm end expiration (B-mode). (**a2**) Diaphragm end inspiration (B-mode). (**b1**) Diaphragm excursion (B-mode). (**b2**) Diaphragm excursion (M-mode). *D* Diaphragm, *L* Lung, *Li* Liver

helpful in identifying pathological excursion or thickening, especially in ventilated patients [12, 13]. It should be noted however, that positive pressure ventilation and positive end-expiratory pressure (PEEP) cause passive displacement of the diaphragm. As follows, it is important keep these limitations in mind when assessing excursion and thickness of the diaphragm.

32.3.1.1 Excursion

Diaphragm excursion is measured from a subcostal view, with a low frequency transducer (e.g., cardiac or abdominal) aimed at the dome of the diaphragm. There, the diaphragm can be visualized as a thin hyperechogenic line. Usually, the right side is more easily visualized due to the liver that acts as an acoustic window. On the left side, air filled bowels can obstruct a clear view, which necessitates visualization from a more dorsolateral point. With inspiration, the diaphragm will move toward the transducer, while with expiration the diaphragm will relax and return to its original position. If quantification of this amplitude is desired, M-mode is commonly used. Normal values in this regard vary strongly (below 1–2.7 cm indicating dysfunction) [14, 15]. For qualitative information, e.g., diaphragm paralysis or patient ventilator asynchronies, B-mode examination can be sufficient.

32.3.1.2 Thickness and Thickening

Diaphragm thickness is measured on the mid-axillary line, approximately between the 8th and 11th intercostal space [12]. This is also referred to as the zone of apposition, as the diaphragm closely lines the chest wall. With a high frequency transducer, the diaphragm appears as a three-layered structure, surrounded by the hyperechogenic pleura and peritoneum, with an additional hyperechogenic layer within the muscle. Calipers for thickness measurements are placed between the pleura and peritoneum. If this measurement is repeated during end-expiration and end-inspiration, the so-called thickening fraction ((thickness end inspiration—thickness end-expiration)/thickness end-expiration) can be calculated. This is seen as a method to quantify diaphragm function and can be used to titrate ventilator settings or guide extubation. In spontaneously breathing ventilated patients, values below 30–36% are viewed as indicative of diaphragm dysfunction [16–18].

32.3.2 Application in Clinical Practice

32.3.2.1 Diaphragm Protective Ventilation

While lung protective ventilation has become general knowledge in critical care practice, the concept of diaphragm protective ventilation is far less known. The underlying concept is to titrate ventilator settings to neither over- nor under assist the diaphragm to prevent disuse atrophy and load-induced injury, respectively (see also Chap. 6). Studies have in fact shown that loss of diaphragm thickness and functionality are associated with worse outcomes, highlighting the importance of this concept [19]. Nevertheless, as values for physiological levels of contraction vary strongly, no cutoffs are defined as of yet that clearly indicate excessive and insufficient effort, making implantation in clinical practice difficult [20]. Additionally, while diaphragm protective ventilation can be seen as complementary strategic goal to lung protective ventilation, these endpoints do not always align. A frequently recurring example might be necessity for deep sedation and paralysis of patients with excessive breathing efforts, which potentially cause harmful pulmonary pressures. While this is beneficial from a lung protective perspective, the diaphragm loses all activity and hence is at risk for quick atrophy [21].

32.3.2.2 Patient Ventilator Asynchrony

Patient ventilator asynchronies arise in the context of inadequate ventilator response to the patient's respiratory needs. It is a frequently occurring, yet also often unrecognized problem. Its timely identification and treatment are important, as asynchronies are associated with worse outcomes and patient discomfort [22]. Sonographic assessment of the diaphragm could be a valuable tool in this regard, but more evidence is needed for implementation in clinical practice. As such, this is not further discussed in this chapter, however we refer the interested readers to a recent review summarizing the important asynchronies and ultrasonographic correlates [13].

32.3.2.3 Weaning

Liberating patients from mechanical ventilation (see also Chap. 22) is a difficult task requiring optimal adaption of lungs, respiratory muscles and heart [1]. With ultrasound, all these systems can be readily assessed and as such offers the possibility to monitor changes during weaning and assess causes of failed attempts. This approach has been summarized in the "ABCD-approach," in which each letter corresponds to a vital process during weaning [13].

(A) Aeration score and pleural effusion: Potential loss of lung aeration is assessed as described above. An aeration score of >17 is associated with post extubation distress [23]. In addition, if B-lines are counted before and at the end of a spontaneous breathing trial in four anterior lung regions, an increase of more than six B-lines is also associated with a failed spontaneous breathing trial [24]. The presence and extent of pleural effusions should also be determined and potentially treated.
(B) Below the diaphragm: Abdominal processes can potentially disrupt ideal respiratory mechanics and as such have an import impact.
(C) Cardiac: Evaluation of cardiac function is a broad term and its extent is largely dependent on expertise of the physician. Straightforward methods include eyeballing left ventricular function and measuring tricuspid annular plane systolic excursion as surrogate for right ventricular systolic function. With more experience, diastolic function can also be determined through e.g., E/A-ratio.
(D) Diaphragm: Percentual change in diaphragm thickness and its excursion are evaluated. Low numbers are associated with extubation failure. More information is provided in the next section.
(E) Extra-diaphragmatic respiratory muscles: Active use of these muscles is indicative of a high respiratory workload or a failing diaphragm. To this end, thickening of the parasternal intercostal muscles and the lateral abdominal muscles can be used [1, 25].

32.3.2.4 Predicting Extubation Outcome

Diaphragm thickening fraction is the most well studied ultrasound parameter for predicting extubation outcome. The first landmark studies identified strong predictive properties, if the cut-off ranges for successful extubation were set above 30–36% [16–18]. Over the last years however, conflicting evidence has arisen, challenging the previous beliefs of it being a good predictor [26, 27]. As such, currently there is no solid basis to provide a recommendation in favor or against its use. In case implementation in clinical practice is desired, the most feasible method seems to be as tool to detect underlying etiology of failed weaning attempts, which is described in the section above.

32.4 Accessory Respiratory Muscles

The accessory respiratory muscles (most importantly lateral abdominal wall muscles, rectus abdominis muscle and intercostal muscles) are an important, yet often neglected part of the respiratory muscle pump. They are vital for effective airway clearance, prevention of atelectasis and assist the diaphragm in situations of high breathing effort [28, 29]. Just as the diaphragm and lungs, they are all relatively easily measured by ultrasound and as such could potentially be included in a complete ultrasonographic assessment of the respiratory system.

Currently, the evidence, while growing, is still scarce and little is known about reference values for distinguishing physiological—from pathological states and concrete implementation in clinical practice [30]. Potential future applications could be found in early detection of high respiratory effort or as predictors or difficult weaning [25].

32.5 Limitations

Ultrasonography of the lungs has limitations that are inherent to the physical properties of ultrasound. As mentioned before, the large difference in impedance between air and tissue causes reflection of all ultrasound waves at air-tissue barriers. Therefore, pulmonary pathology can solely be detected if it reaches the pleura. In addition, surgical dressings or any other physical barriers like subcutaneous emphysema can also limit its utility. For diaphragm ultrasound, limitations lie in alteration of movement and thickening as consequence of being mechanically ventilated as well as the need to use a skin marker for ensuring reproducibility of the measurements over different days and operators. As such, carefully evaluating ventilator settings is crucial when interpreting measurements. For both lung and diaphragm ultrasound it should also be noted, that being able to correctly interpret images requires some experience. In the hands of beginners, imaging can give a false sense of security and pathology can be easily missed.

32.6 Conclusion

In this chapter, we outlined the basic concepts of ultrasonographic assessment of the respiratory system and its application in clinical practice. Together with knowledge from the previous chapters of respiratory physiology, it can be a powerful tool to aid the intensivist in monitoring mechanically ventilated patients. It serves as diagnostic and monitoring tool for pulmonary pathology, patient ventilator asynchronies and potentially even allows guidance in titrating ventilator settings.

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Electrical Impedance Tomography

33

Inéz Frerichs

33.1 Introduction

Electrical impedance tomography (EIT) is an imaging method invented in the early eighties of the last century [1]. The first 20 years of its development were dominated by research activities accomplished by biomedical and electrical engineers, physicists, mathematicians and physiologists. The main focus was on the technological refinement of the method and its validation.

Two factors have decisively influenced the later development of EIT and led to its increasing clinical acceptance and use, mostly for monitoring of patients undergoing ventilator therapy. The first factor was the clinical need for the type of information provided by EIT and the second one was the maturation of the technology which allowed reliable patient examinations in a clinical setting with approved EIT devices.

When used on the chest, EIT enables the measurement of instantaneous changes of regional lung ventilation and aeration. This information became clinically relevant since the understanding that mechanical ventilation was not just a life-saving therapy but also the cause of ventilator-associated lung injury and that factors contributing to the development of pulmonary biotrauma, like alveolar overdistension, atelectasis and cyclic tidal recruitment and collapse, played a crucial role in promoting it.

Efforts have been therefore undertaken to minimize the injurious effects of mechanical ventilation by adopting lung-protective ventilation strategies with new modes of ventilation and extended patient monitoring. Nonetheless, the information on the immediate effects of mechanical ventilation on regional filling of lungs with

I. Frerichs (✉)
Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany
e-mail: inez.frerichs@uksh.de

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air, the dynamic distribution of air during the respiratory cycle or the regional ventilation-perfusion matching was still not available at the bedside. This information is relevant because of the physiological spatial and temporal inhomogeneity of lung ventilation, aeration and perfusion, which is further modified by factors like age, posture, lung diseases and, ultimately, treatment, including mechanical ventilation.

By providing real-time information on regional lung ventilation, aeration, respiratory mechanics and perfusion, as well as on the presence of the deleterious events of overdistension, atelectasis and tidal recruitment and collapse, EIT creates an instantaneous feedback on the patient's functional lung status as well as on the adequacy of the chosen ventilator settings. By identifying the direct local effects of the set ventilation on the lung tissue, EIT provides guidance to personalized and optimized ventilator therapy.

This chapter is dedicated to chest EIT and its use in monitoring of mechanically ventilated patients. It first describes the measuring principle of EIT and explains how EIT examinations are carried out. Then the methods of EIT data analysis are addressed and details provided on the generation of derived functional EIT images and numerical EIT measures. Finally, the use of this information in a clinical setting is explained, including a few clinical examples.

33.2 EIT Basics

The general principle of EIT is based on the measurement of electrical bioimpedance. Electrical bioimpedance is a tissue property defined as the measure of tissue opposition to propagation of an alternating electrical current. Hence, EIT probes the body by application of very small imperceptible electrical currents and measures the resulting voltages on its surface.

The excitation current needs to be applied at more than just one location on the chest to render sufficient information for the generation of images of the intrathoracic distribution of electrical bioimpedance. Hence, an array of electrodes is placed on the chest circumference, either in a transverse or a slightly oblique plane (Fig. 33.1, top). The current commercial EIT devices use arrays of either 16 or 32 electrodes. The electrodes are integrated into belts, vests or stripes, whereas the early devices used single self-adhesive electrodes.

The electrical currents, with a typical amplitude of a few mA and frequency of about 50–200 kHz, are applied consecutively through different pairs of electrodes. During each single current application, the resulting voltages are measured at all the other passive electrode pairs on the chest. The raw data acquired during one complete cycle of rotating current applications and voltage measurements are called the "frame". One frame of data is needed to generate one primary EIT image. The frame (i.e., scan) rate of an EIT device gives the number of primary EIT images that can be obtained per second. The scan rate of current EIT devices is about 50 images per second.

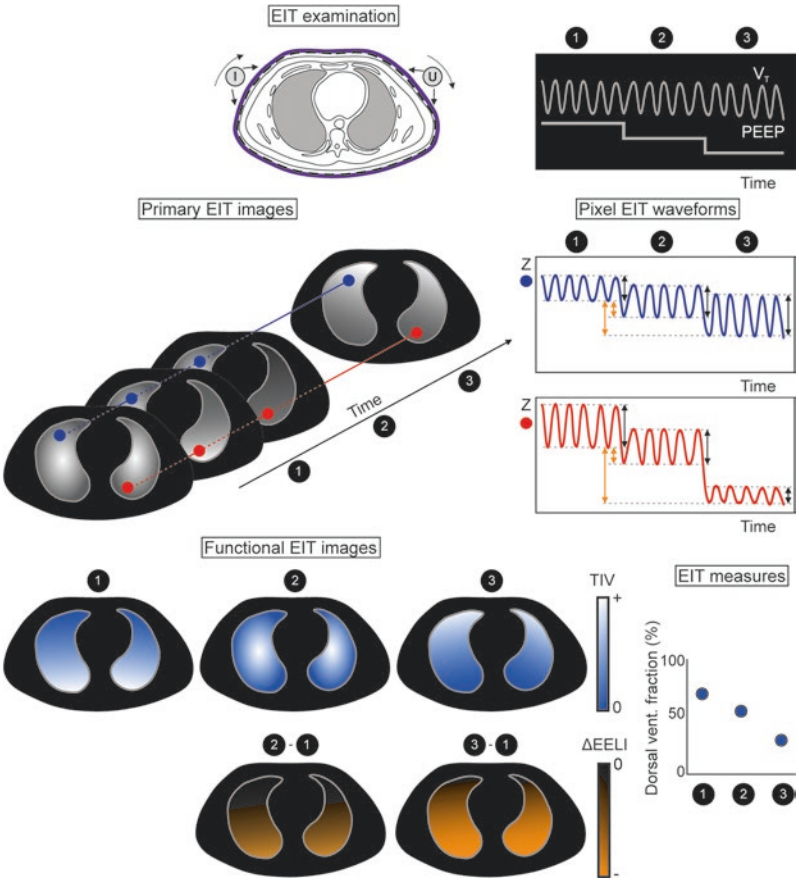

Fig. 33.1 Schematic drawing highlighting the measuring principle of electrical impedance tomography (EIT) and the different steps in EIT data acquisition and analysis. During an EIT examination (*top left*), an EIT interface with integrated electrodes (*violet line with short black bars*) is placed around the chest. The electrodes are needed for rapid short applications of minute alternating electrical currents (I) and measurements of resulting voltage (U) differences, both processes are rotating around the chest. EIT data can be acquired in the course of mechanical ventilation, e.g., during example ventilation with a constant tidal volume (V_T) at three levels of positive end-expiratory pressure (PEEP) (*top right*). The raw EIT data render a series of primary EIT images (*middle left*). Two image pixels are highlighted, one is in the nondependent right lung (*blue*), the other in the dependent left lung region (*red*). Regional pixel electrical impedance (Z) waveforms (*middle right*) show the dissimilar amplitudes of tidal impedance variation (TIV) (*black arrows*) in the selected pixels during the three examination phases. The changes in end-expiratory lung impedance (ΔEELI) between the first and the other two phases are also shown (*orange arrows*). The calculated values of TIV and ΔEELI in all pixels can be plotted in their respective positions, thereby creating two different types of functional EIT images (*bottom left*). The top blue-white images show the spatial distribution of V_T, the bottom black-orange ones the regional fall in end-expiratory lung volume. The values presented in functional images can serve the calculation of derived quantitative EIT measures. One such example measure is the dorsal fraction of ventilation, i.e., the proportion of TIV in the dorsal half of the image relative to the whole image. Its values in the three examination phases are given in the diagram (*bottom right*)

The primary EIT images are two-dimensional plots of regional (pixel) values of electrical bioimpedance calculated from a series of data frames (Fig. 33.1, middle left) in a process called image reconstruction. (It needs to be mentioned that current EIT devices do not generate images of absolute electrical bioimpedance values but of relative impedance differences in relation to reference impedance. Thus, EIT data are dimensionless and often given in "arbitrary units".) The EIT images typically consist of about 1000 pixels, depending on the used image reconstruction algorithm.

The electrical impedance of lung tissue depends on its air, blood and fluid content as well as on the cellular barrier integrity. Hence, all physiological and pathological processes affecting them can be determined by EIT. The largest impedance changes are elicited by changes in air volume, which explains why EIT is mainly used for monitoring of regional lung ventilation and aeration. Higher air volume distends the lung tissue whereby the pathways, through which the applied current needs to pass, elongate and the measured impedance increases. The fall in regional air volume has an opposite effect. Increased volume of blood in the lungs during systole decreases the measured electrical impedance because of the high blood conductivity. Administration of electrolyte solutions during intravenous fluid therapy results in an overall fall of lung impedance whereas local accumulation of fluid, like in pleural effusion, leads to its regional fall.

The knowledge of the basic principles of EIT and the factors affecting the measured electrical impedance may assist the user in correct interpretation of EIT findings.

33.3 Patient Examination Using EIT

EIT is a safe and noninvasive imaging method with no known hazards. There exist only a few contraindications to its use, like large chest wounds or multiple intrathoracic drainages that render the correct positioning of the electrode interface on the chest impossible. EIT examinations are also not recommended in patients with implanted active medical devices, like pacemakers and defibrillators. Application of EIT in mechanically ventilated patients in operating rooms is possible, however, the EIT devices should be disconnected during electrocautery.

EIT examination starts with the placement of the electrode interface on the chest. The interfaces are vendor-specific and usually made from silicone or textile fabric either for repeated or single use with the electrodes integrated in the material. EIT electrodes must have a good contact with the skin. Therefore, an electrode interface matching the individual patient chest circumference should be chosen. The electrode interfaces are available in different sizes suitable for chest girths between about 17 and 150 cm. Depending on the type of electrode interface, the contact may be improved by moistening using water, saline solution, electrode gel or specific contact sprays. The electrode interfaces should not be placed in a too caudal location, below the sixth intercostal space. This is important especially when the patients are examined in the lying postures. EIT monitoring can be started immediately after

the electrode interface is placed on the chest, however, a short delay of a few minutes is recommended to allow the electrodes to warm up.

Once EIT monitoring is commenced, the data acquisition may run continuously for up to 24–72 h, depending on the device used. It is the user's decision to determine whether such long monitoring is meaningful or whether shorter times of EIT use are not more convenient and suitable for the clinical question that the user intends to solve by EIT. For instance, if a too deep position of an uncuffed endotracheal tube in the main bronchus is postulated in a ventilated neonate, then a few minutes of EIT recording are sufficient to identify whether the tube repositioning improves the ventilation distribution in the chest. If a decremental positive end-expiratory pressure (PEEP) trial is conducted with the aim of establishing the "optimum" PEEP then a recording of little below half an hour is needed. If the effect of prone position on regional lung recruitment is assessed then an examination lasting more than 1 h is meaningful. Finally, if a preterm neonate with infant respiratory distress syndrome is treated with surfactant and the evolution of ventilation and aeration needs to be closely monitored and the potential occurrence of pneumothorax immediately identified, then continuous long-term EIT monitoring lasting hours or even days may be selected.

33.4 Assessment of Regional Lung Ventilation and Aeration Changes by EIT

The series of primary EIT images acquired during ventilation capture the instantaneous changes in regional electrical impedance. These ventilation-related changes can be visualized in real time, as a dynamic image stream or in form of waveforms. The pixel impedance waveforms (Fig. 33.1, middle right) form the basis for further analyses. For visualization purposes, they can be summed up over the whole image and presented as "global" impedance waveform or in regions-of-interest, typically quadrants, ventrodorsal layers, or image halves in real time.

The pixel, ROI and global impedance waveforms allow the analysis of regional tidal impedance variation (TIV), corresponding to regional tidal volume (V_T), and of changes in regional end-expiratory lung impedance (ΔEELI), reflecting mainly the shifts in end-expiratory lung volume (EELV). As illustrated in the schematic Fig. 33.1 (middle right panel), there exist regional differences in pixel TIV and ΔEELI. During this example recording, PEEP value is reduced twice during volume-controlled ventilation. The EIT waveform originating from an image pixel in the nondependent lung region shows the lowest TIV at the highest PEEP. This is caused by regional overdistension with reduced compliance. In the later course, TIV increases with decreasing PEEP because the overdistension is relieved. In contrast, the waveform originating from a pixel in the dependent region reveals the falling amplitude of TIV with decreasing PEEP because of de-recruitment. This alveolar collapse is also evidenced by a massive decrease in ΔEELI after the second PEEP change.

If the pixel values of TIV, calculated from these three phases of an example EIT examination, are plotted at their respective locations, then the resulting color-coded maps, called "functional" EIT images, present the distribution of V_T in the chest cross-section (Fig. 33.1, bottom left, top three images). At the highest PEEP, inspired air is preferentially directed to the dependent lung region because of ventral overdistension. The ventilation distribution becomes more homogeneous after the first PEEP reduction. The second reduction leads to dorsal collapse and inhomogeneous ventilation distribution favoring the nondependent lung regions. Functional EIT images of another type arise when the pixel values of ΔEELI are plotted in maps with a different color-scale (Fig. 33.1, bottom left, bottom two images). They highlight the reduced regional lung aeration with decreasing PEEP that is more pronounced in the dependent regions.

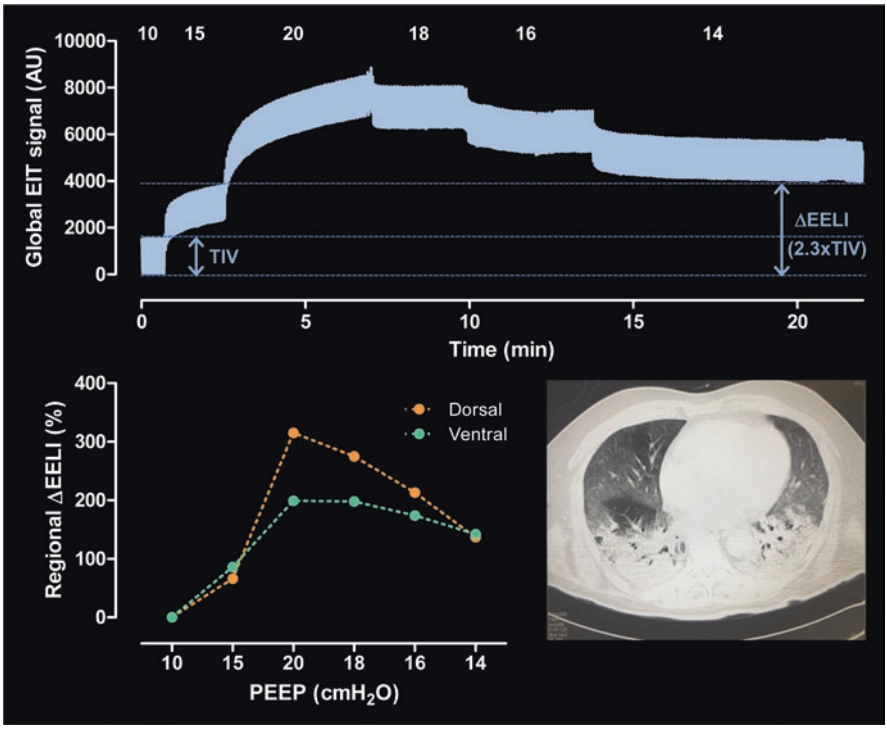

Fig. 33.2 A global (i.e., whole image) EIT signal waveform in arbitrary units (AU) acquired in a supine 64-year-old man suffering from COVID-19-related ARDS during two incremental and four decremental steps in positive end-expiratory pressure (PEEP) (*top*). The EIT examination took place on the second day of ICU admission. The blue arrows show the amplitude of tidal impedance variation (TIV) during ventilation at the initial PEEP value and the change in end-expiratory lung impedance (ΔEELI) at the last PEEP value compared with the beginning of the maneuver. The numbers above the waveform present the set PEEP values in cmH_2O. The ΔEELI values in the ventral and dorsal lung regions relative to the initial values at the lowest PEEP (*bottom left*) demonstrate the more pronounced increase in the dependent regions, implying recruitment. Chest CT scan (*bottom right*) was obtained on the first day of ICU admission. (Reproduced from [2])

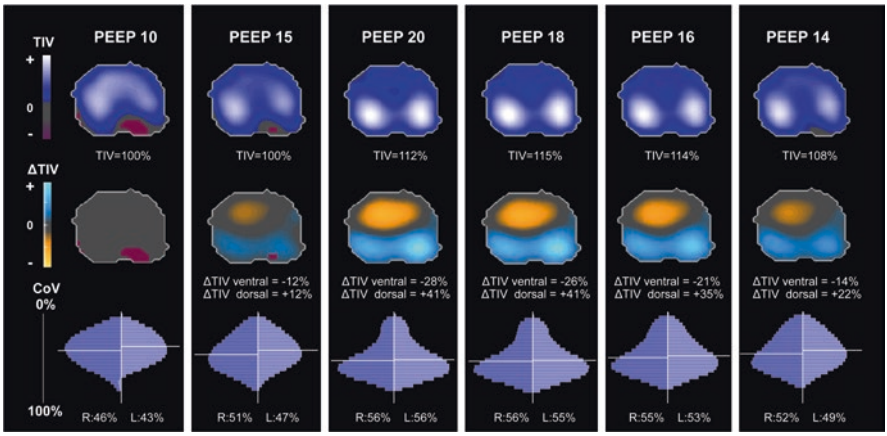

Fig. 33.3 The analysis of regional lung ventilation in a supine patient with COVID-19-related ARDS using EIT. The examination, shown also in Fig. 33.2, was performed during two incremental and four decremental steps in positive end-expiratory pressure (PEEP). Functional EIT images of regional tidal impedance variation (TIV) (*top*) show the distribution of tidal volume in the chest cross-section. Ventilated areas are presented in white and blue colors, the numbers below the images give the global sums of TIV values in percent of initial value at PEEP of 10 cmH_2O. Functional EIT images of regional changes in TIV (ΔTIV) (*middle*) highlight the local increases (light blue areas) and decreases (orange areas) in ventilation at individual PEEP values in comparison with the initial lowest PEEP. The numbers below the images specify the relative changes in TIV in ventral and dorsal lung regions in comparison with the initial TIV distribution at the start of the maneuver. Ventilation profiles (*bottom*) show the distribution of ventilation in the right and left lung regions along the ventrodorsal chest diameter. White horizontal lines in each profile indicate the location of the center of ventilation (CoV) with the corresponding values plotted below each profile. Values smaller than 50% imply preferential ventilation distribution toward ventral regions. (Reproduced from [2])

Figures 33.2 and 33.3 show a clinical case of EIT monitoring in a patient with COVID-19-associated ARDS. A recruitment maneuver increased lung aeration (see the global EIT waveform in Fig. 33.2, top), which fell stepwise during the subsequent PEEP reduction. Nonetheless, a large aeration win was present by the end of the maneuver. ΔEELI in the ventral and dorsal region (Fig. 33.2, bottom left) demonstrated the higher aeration gain in the dorsal region. The top functional EIT images in Fig. 33.3 show how the ventilation was distributed during the respective phases of this patient's examination, with reduced dorsal ventilation in the beginning, improved dorsal ventilation at the highest PEEP (with simultaneous reduction in ventral regions) and relatively homogeneous ventilation distribution at the final decremental PEEP step.

Functional EIT images of regional TIV distribution are frequently subjected to further quantitative analyses, aiming to describe the homogeneity of ventilation distribution by numerical measures. One simple and intuitive approach is to calculate the fraction of ventilation in the dorsal regions, which in the theoretical example given in Fig. 33.1 (bottom right) indicates the progressive reduction in ventilation in the dependent regions. A clinical case (Fig. 33.4d) shows the low ventilation in the

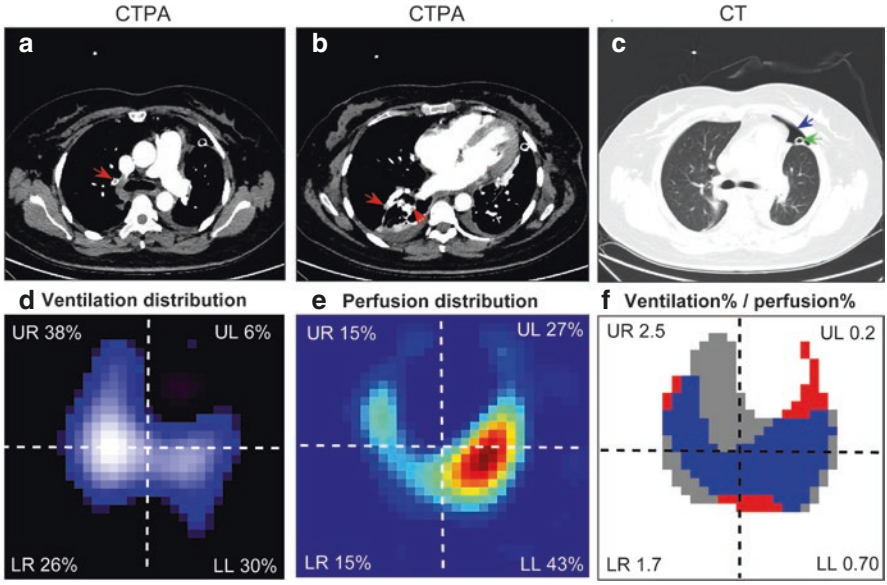

Fig. 33.4 Computed tomography (CT), CT pulmonary angiography (CTPA), and electrical impedance tomography (EIT) results showing ventilation and perfusion defects in a 47-year old supine woman 1 day after thoracic surgery. CTPA demonstrated multiple emboli in the right pulmonary artery branches (*red arrows in panels* **a** *and* **b**). Small pneumothorax in the left ventral region was detected in the CT scan (*blue arrow in panel* **c**). The position of the drainage tube in the thoracic cavity is indicated (*green arrow*). Functional EIT image of ventilation distribution (**d**) shows the low-ventilated regions in dark blue and the high-ventilated regions in white. The values in the image corners give the percentage of ventilation in the corresponding quadrant. Functional EIT image of perfusion distribution shows the regions with high perfusion marked in red and low perfusion in blue (**e**). The values give the percentage of perfusion in the corresponding quadrant. Functional EIT image showing the distribution of regional ventilation/perfusion ratios (**f**) uses the following annotation: regions with high ventilation and low perfusion are marked in gray (corresponding pixels show the ventilated but not perfused regions), low-ventilation and high-perfusion regions in red (corresponding pixels show the perfused but not ventilated regions), and good ventilation–perfusion matching in blue (pixels belong to both regions and exhibit both ventilation and perfusion). Regional ventilation%/perfusion% ratios shown in each quadrant correspond to ventilation distribution (in %) over perfusion distribution (in %) in the corresponding quadrant. *LL* lower left lung, *LR* lower right lung, *UL* upper left lung, *UR* upper right lung. (Reprinted from [3] with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved)

image quadrant representing the left ventral lung due to a pneumothorax. A different approach is to determine the dispersion of pixel TIV values, e.g., by the coefficient of variation or the global inhomogeneity index [4]. An additional parameter, allowing the assessment of ventilation distribution in the right-to-left and ventrodorsal directions, is the center of ventilation. Figure 33.3 (bottom) illustrates how the value of this parameter calculated over the right and left image halves shifted from ventral toward dorsal regions during the recruitment and reached a relatively center position by the end of the examination.

Thanks to its high scan rate, EIT also allows the dynamic assessment of regional filling and emptying of air in the lungs, either during tidal breathing or specific maneuvers, like the constant low-flow inflation and deflation. The intratidal or intrainflation/deflation analysis of regional impedance waveforms, enables the calculation of regional delay in ventilation onset [5], regional respiratory time constants [6] or pendelluft [7]. When combined with airway pressure measurement, regional respiratory compliance [8, 9] and regional opening and closing pressures [10] can be determined.

Generally, EIT is very robust in determining ventilation-related impedance variation and the parameters derived from tidal ventilation and specific maneuvers are reproducible and reliable. The EIT users should however be cautious when interpreting the ΔEELI parameter which need not reflect merely changes in EELV but may be impacted by other effects, like fluid therapy [11], patient movement [12], or fluctuating electrode-skin contact during pulsation therapy [13].

The progress in ventilation monitoring by EIT is documented in numerous narrative and systematic reviews (e.g., [14–20]) and by the expert consensus statement on chest EIT [17]. Recent prospective clinical studies in ARDS patients demonstrated for the first time the use of an EIT-based protocol for personalized PEEP finding in a randomized study design [21] and for setting of both PEEP and V_T [22].

33.5 Assessment of Regional Lung Perfusion by EIT

Heart action leads to periodic changes in pulmonary blood volume and to heart-beat synchronous variation of regional electrical bioimpedance that can be recorded by EIT. Although this EIT signal component has been used to assess regional perfusion, its amplitude is low and it is less specific to flow than an approach based on the administration of a bolus of hypertonic saline solution. The saline bolus serves as a contrast agent and allows EIT to generate pixel dilution curves and measure regional blood flow [23]. Functional EIT images of regional perfusion can be generated (Fig. 33.4, bottom middle) and compared with the ventilation images, allowing the assessment of regional ventilation-perfusion matching (Fig. 33.4, bottom right). Recent clinical studies confirmed the safety and reliability of this method in patients and documented the association of ventilation-perfusion mismatch with adverse outcomes [24, 25]. The limitations of this method are that it is discontinuous and requires the central-venous saline bolus application during a breath-hold.

33.6 Summary

EIT monitoring provides a unique real-time continuous information on regional lung function at the bedside. It allows early identification of changes in the patient's status and personalized adjustment of therapy and care. In association with other monitoring methods it enables a comprehensive assessment of the effectiveness and invasiveness of mechanical ventilation. The information on the homogeneity of

ventilation and perfusion distribution, the presence of deleterious phenomena like alveolar overdistension, atelectasis formation, cyclic opening and closing, the occurrence of ventilation-perfusion mismatch, pendelluft or pneumothorax generates inputs needed for adequate guidance and optimization of ventilator therapy. The clinical acceptance and extent of EIT use would benefit from standardized examinations, including protocols for EIT application in specific clinical situations, automated goal-oriented analyses and provision of decision-support tools.

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Esophageal Pressure Monitoring

34

Evangelia Akoumianaki and Katerina Vaporidi

Esophageal pressure (Pes) is the pressure measured at the lower part of the esophagus and it is used as a surrogate for the pressure inside the pleural space (Ppl) [1]. Monitoring of Pes enables the evaluation of the forces applied across the lungs, the mechanical properties of the lungs and chest wall, and the pressures generated by the respiratory muscles.

34.1 Technique

Esophageal pressure is measured by inserting an air-filled balloon catheter into the esophagus similarly to a nasogastric tube. Several esophageal balloon catheters are commercially available and monitoring of Pes is obtained by connecting the opening of the catheter to an air-filled pressure transducer connected to a dedicated acquisition system or a standard patient's monitor or mechanical ventilator. A reliable Ppl estimation via the esophageal catheter requires proper balloon inflation and position, and relatively uniform distribution of pressures in the pleural cavity. At the ideal position of the balloon, where Pes reflects Ppl, the ratio between Pes and Paw variation (ΔPes/ΔPaw) during airway occlusion should be close to 1, Pes tidal swings should resemble tidal volume swings, and Pes and tidal volume relationship should be linear [2].

The technique to insert and check the proper filling and position of the esophageal catheter (Baydur's test) is described in Fig. 34.1. An overfilled balloon accurately transmits Pes changes but overestimates Pes absolute values. An underfilled balloon underestimates both absolute values and respiratory Pes swings. At its optimal filling volume, the balloon does not generate elastic recoil pressure. This

E. Akoumianaki · K. Vaporidi (✉)
Department of Intensive Care, University Hospital of Heraklion and School of Medicine, University of Crete, Heraklio, Greece

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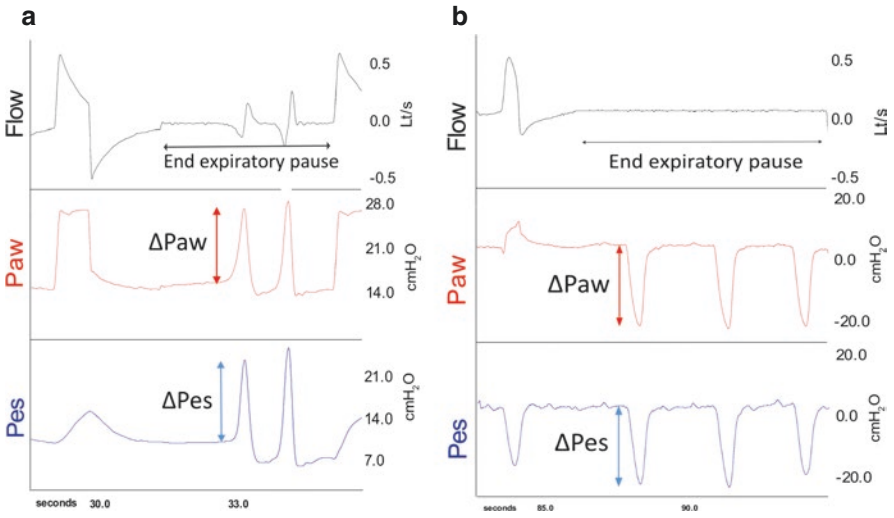


Fig. 34.1 Placement of the esophageal catheter and assessment of proper balloon filling and position. The esophageal catheter is placed like a nasogastric tube, trans-nasally or trans-orally, usually at a depth of 40–55 cm. The distal part is attached to a pressure transducer and the balloon is inflated with air. The balloon position in the esophagus is recognized from the presence of respiratory and cardiac oscillations in Pes. The balloon filling involves the following steps: (1) complete deflation of the balloon, to precisely calculate the volume inflated, (2) equilibration at atmospheric pressure via brief disconnection, (3) injection of the maximum allowed air volume (specific to each balloon) to homogeneously unfold the balloon, (4) deflation at the recommended volume. The filling volume can be further optimized by a stepwise (0.5 mL) inflation of the balloon, selecting the lowest volume associated with the largest tidal swings of Pes. The proper position of the balloon is subsequently confirmed by comparing Paw swings to Pes swings in response to maneuvers during an end-expiratory airway occlusion: at a constant lung volume, the transpulmonary pressure does not change and hence Pes changes should equal Paw changes and vice versa. Ideally, the ΔPes/ΔPaw should be close to 1, but a ratio of 0.8–1.2 is considered acceptable. From top to bottom, flow, airway pressure (Paw), and esophageal pressure (Pes) tracings over time. (**a**) In control mode, two gentle pressures on the chest during an end-expiratory pause generate similar positive deflections in Paw and Pes (red and blue arrows). (**b**) In assisted mode (here in pressure support), during an end-expiratory pause, patient's inspiratory efforts against the occluded airway produce similar negative deflections in Paw and Pes (red and blue arrows)

volume differs among commercially available catheters, depending on their length, diameter, and compliance, but also on the pressure surrounding the balloon [1, 2]. Larger and longer balloons have higher filling volumes and broader range of optimal volumes, making precise measurements easier [1]. It is noteworthy that the inflation volumes suggested by the manufacturers were validated under atmospheric pressures. Nevertheless, when pleural pressure is negative, such as during spontaneous breathing, balloons may need lower than recommended filling volume, while as pleural pressure increases (high PEEP, ΔP), the optimal filling volume can be higher than recommended [1, 2]. It is important to periodically check the filling volume, especially following significant changes in intrathoracic pressures. Occasionally, Pes may be falsely elevated at the lower third part of the esophagus, due to the

superimposed pressure from the mediastinum and the diaphragm, resulting in ~5 cmH_2O overestimation of Ppl at midlung height [1, 2].

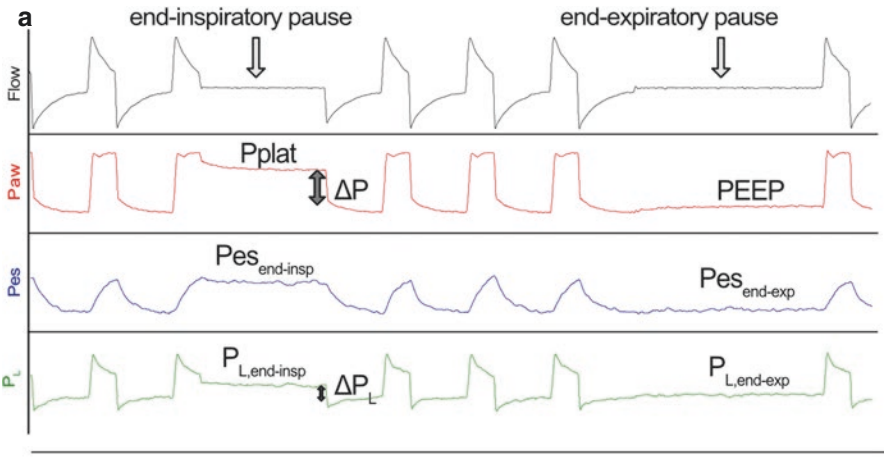
Moreover, the use of Pes as a substitute of Ppl, assumes that Ppl is similar everywhere in the pleural cavity and that changes in Ppl are uniformly distributed in the pleural space. Notwithstanding, static Ppl increases by 0.25 cmH_2O/cm from the nondependent to dependent lung regions due to gravitational forces in the healthy lungs, and almost doubles, reaching 10 cmH_2O in patients with Acute Respiratory Distress Syndrome (ARDS) [3]. In any patient position, the value of Pes reflects Ppl of the mid to dependent lung regions [1, 2]. Experimental data suggest that, in injured lungs, tidal changes in Ppl may be greater in the dependent than the nondependent lung regions [4], but remain similar between injured and non-injured lungs in asymmetrical lung injury [5].

34.2 Measurements of Pes-derived Variables

34.2.1 Transpulmonary Pressures

The transpulmonary pressure (P_L) is the pressure difference across the lung. Under passive, static (no flow) conditions, P_L equals the elastic recoil pressure of the lung, assuming that alveolar and airway pressures equalize (when there is no airway collapse) [6]. The elastic recoil pressure of the lung is the actual pressure distending the lung. Static P_L at the end of inspiration ($P_{L,end\text{-}insp}$) and expiration ($P_{L,end\text{-}exp}$), can be calculated during an end-inspiratory and end-expiratory occlusion maneuver as shown in Fig. 34.2. Alternatively, transpulmonary pressures can be estimated from airway pressures multiplied by the ratio of the lung to respiratory system elastance, to overcome the shortcomings of Pes absolute values [1, 2]. The assumptions of this elastance-derived method are that Ppl, P_L and Paw are zero (atmospheric) at end-expiration and that elastance is linear during the breath. However, in critically ill patients Palv and Ppl are often higher than zero (airway closure in recumbent position, active expiration, alveolar flooding), and the pressure-volume relationship may not be linear, particularly in ARDS. The direct and the elastance-derived methods provide significantly different P_L values and it remains controversial which method is preferable in clinical practice [7]. A study in human cadavers showed that directly measured $P_{L,end\text{-}exp}$ was accurate and could be used to titrate PEEP, while the elastance-derived $P_{L,end\text{-}insp}$ better represented the true P_L at end-inspiration of the nondependent regions [8].

A high $Pes_{end\text{-}exp}$ associated with negative $P_{L,end\text{-}exp}$ may be occasionally found in critically ill patients. This P_L does not represent the elastic recoil pressure of the lung for several possible reasons: first, $Pes_{end\text{-}exp}$ can be overestimated due to the mediastinum's weight, and subtraction of 5 cmH_2O from measured Pes has been proposed; second, the distribution of Ppl across the pleural space can be uneven, with Pes reflecting Ppl only at midlung height, while at nondependent lung regions Ppl is lower and P_L positive; third, collapsed/flooded alveoli prevent Palv and Paw equilibration, and Palv equals local Ppl [9].



$$P_L = Paw - Pes \qquad P_L = Paw \times E_L/E_{RS}$$

$$E_{RS} = \Delta P/VT \quad E_L = \Delta P_L/VT \quad E_{CW} = \Delta Pes/VT$$

$$\Delta P_L = P_{Lend\text{-}insp} - P_{Lend\text{-}exp} \qquad \Delta P_L = \Delta P \times E_L/E_{RS}$$

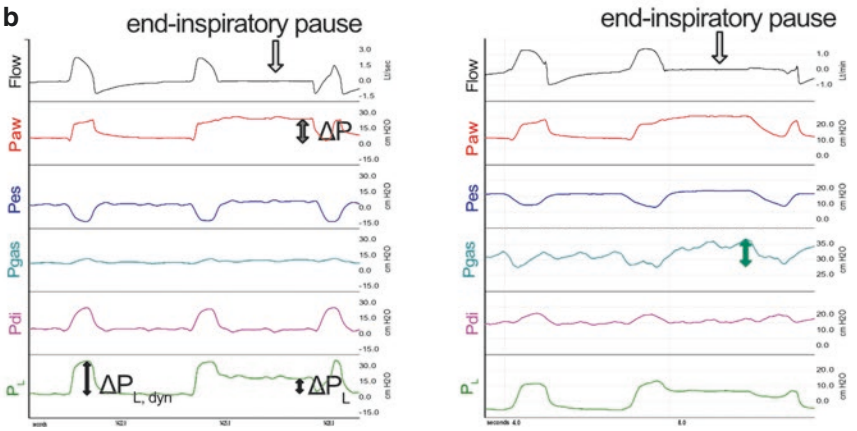


Fig. 34.2 Transpulmonary pressures and lung mechanics calculation during controlled mechanical ventilation (**a**) and assisted (**b**) mechanical ventilation. (**a**) From top to bottom, flow, airway pressure (Paw), esophageal pressure (Pes) and transpulmonary pressure (P_L) tracings over time in a passively ventilated patient. The P_L is calculated as the difference between Paw and Pes. An end-inspiratory and an end-expiratory occlusion maneuver are shown. During an airway occlusion the Palv equilibrates with Paw, assuming that all airways are open. Therefore, in the absence of respiratory muscle activity, Paw during end-inspiratory (Pplat) and end-expiratory occlusion maneuvers (PEEP) are deemed similar to static end-inspiratory and end-expiratory Palv, respectively. The elastic recoil pressure of the lung (P_L when flow is zero) is the actual pressure applied to the lung at each lung volume above the functional residual capacity. Using the absolute Pes values, static end-inspiratory P_L ($P_{L,end\text{-}insp}$) and end-expiratory P_L ($P_{L,end\text{-}exp}$), can be calculated as illustrated. The driving pressure of the respiratory system (ΔP) can be calculated from the difference of Pplat and PEEP, and the elastance of the respiratory system (Ers) is the ratio between ΔP and VT. Pes calculation permits the partition of Ers to the elastance of the lung (E_L) and that of the chest wall (E_{CW}) as illustrated. ΔP_L is called the driving pressure of the lung and reflects the change in lung stress due to VT. The transpulmonary pressures can also be calculated as the product of Paw times the ratio between E_L and Ers (elastance-derived method). Hence, only changes in Pes and not absolute values are required for this method. B. From top to bottom, flow, airway pressure (Paw), esophageal pressure (Pes), gastric pressure (Pgas), transdiaphragmatic pressure (Pdi) and dynamic transpulmonary pressure (P_L) tracings over time in a spontaneously breathing patient during pressure support. Transdiaphragmatic pressure is calculated by subtracting Pes from Pgas. An end-inspiratory pause is performed to calculate static end-inspiratory airway (Pplat) and transpulmonary ($P_{L,end\text{-}insp}$) pressures. In the left panel, the absence of respiratory muscles contraction guarantees reliable Pplat and ΔP measurement, while in the right panel, expiratory muscles contraction, indicated by the Pgas rise during the occlusion (green arrow), Pplat and ΔP measurements are not valid

During assisted mechanical inflation the dynamic P_L equals the difference between the positive Paw and the negative Pes (Fig. 34.2), and represents both the elastic and resistive pressure component. Static end-inspiratory and end-expiratory P_L cannot be reliably assessed because airway occlusion maneuvers do not guarantee relaxation of respiratory muscles. Expiratory muscle activity can be recognized by measuring gastric pressure.

34.2.2 Indices of Inspiratory Effort and Dynamic Hyperinflation

The gold standard measurements of inspiratory effort include the pressure-time product (PTP) of Pes (for all respiratory muscles) or transdiaphragmatic pressure (for the diaphragm), and the work of breathing, both computed using Pes, as shown in Fig. 34.3. The pressure generated by all respiratory muscles (Pmus) is, at any time, the difference between the static elastic recoil pressure of the chest wall (Ecw) and Pes. The Ecw can be measured either under static conditions from the tidal changes in Pes, assuming that it remains unchanged between static and active breathing, or estimated to be equal to 4% of the predicted vital capacity per cmH_2O. The pressure generated by the diaphragm, the transdiaphragmatic pressure (Pdi), is estimated by subtracting Pes from gastric pressure (Pgas), which in turn can be measured like Pes by placing a balloon catheter in the stomach.

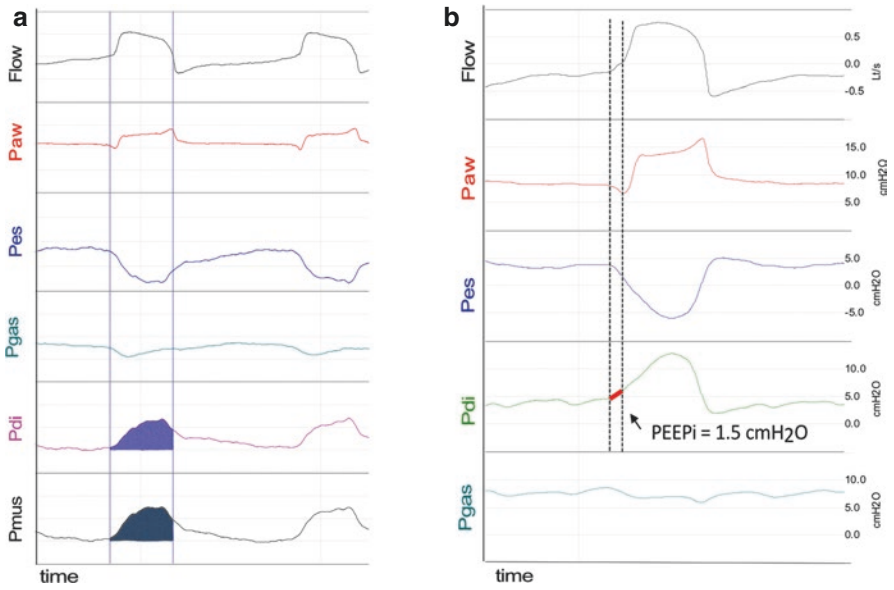


Fig. 34.3 Calculation of Pressure-time-product and intrinsic PEEP. (**a**) Calculation of pressure-time (PTP) product during pressure support ventilation. From top to bottom, flow, airway pressure (Paw), esophageal pressure (Pes), gastric pressure (Pgas), transdiaphragmatic pressure (Pdi) and muscle pressure (Pmus) tracings over time during pressure support ventilation. The pressure generated by the diaphragm, Pdi can be computed as the difference between gastric and esophageal pressure (Pdi = Pgas − Pes). The pressure generated by all respiratory muscles (Pmus) can be computed as: Pmus = $V * E_{CW}$ − Pes, where V is the instant volume and E_{CW} the chest wall elastance, measured in passive conditions or estimated by formulas. The area under the Pmus or Pdi waveform during inspiration (shaded area) is the PTP per breath of the corresponding pressure. The pressure-time product per minute (PTP/min) can be estimated by multiplying the PTP/*b* with the respiratory rate. Estimation of Pmus and PTP_{Pmus} with this method is valid in the absence of expiratory muscle contraction. (**b**) Calculation of intrinsic PEEP (PEEPi). From top to bottom, flow, airway pressure (Paw), esophageal pressure (Pes), transdiaphragmatic pressure (Pdi) and gastric pressure (Pgas) tracings over time during pressure support ventilation. PEEPi is calculated as the change in Pdi or Pes from the beginning of inspiratory effort to the point of zero flow (dotted lines). It should be noted that, in the presence of expiratory muscle activity, the drop in Pes from the onset of inspiratory effort to the point of zero flow includes the relaxation of expiratory muscles and leads to overestimation of PEEPi, so the change in Pdi should be used instead

The integral of the product of Pmus and tidal volume is used to measure the work of breathing per breath (WOB) in joules and can be expressed per liter or per minute [1]. The magnitude of negative Pes swings during spontaneous breathing also roughly reflects the magnitude of inspiratory muscles effort (see also Chap. 6). The evaluation of Pgas and Pdi enables the evaluation of expiratory muscle contraction and quantification of dynamic hyperinflation through the measurement of intrinsic PEEP (PEEPi) as shown in Figs. 34.2c and 34.3b.

34.3 Monitoring Esophageal Pressure to Guide Mechanical Ventilation

Esophageal pressure monitoring can be implemented intermittently or continuously during mechanical ventilation. The evaluation of transpulmonary pressures and patient's effort can provide valuable information and facilitate individualized titration of ventilator settings. The following section presents the use of Pes-derived variables in titration of ventilation to achieve the goals of lung and diaphragm-protective ventilation [10, 11], which include: (a) avoiding end-expiratory lung collapse, (b) minimizing alveolar overdistension, (c) optimizing patient–ventilator interaction.

34.3.1 Monitoring $P_{L,end\text{-}exp}$ for PEEP Titration to Prevent Alveolar Collapse

A relevant goal of PEEP titration, and particularly challenging in ARDS patients, is to prevent alveolar collapse at end-expiration, while avoiding overdistention and hemodynamic compromise. PEEP titrated to a $P_{L,end\text{-}exp}$ of 2–4 cmH_2O has been shown to minimize alveolar collapse in both experimental and clinical settings [8, 12]. The first study in ARDS patients [13] using PEEP titration based on end-expiratory transpulmonary pressure, according to a predefined $P_{L,end\text{-}exp}$-FiO_2 table, was associated with higher set PEEP, improved oxygenation and compliance. In a larger, multi-center study in ARDS patients [14], the implementation of the same $P_{L,exp}$-guided PEEP titration protocol, but a different, high-PEEP—FiO_2 titration table in the control group, was neither associated with differences in PEEP settings, nor with improved survival or liberation from mechanical ventilation than standard-of-care, although less patients in intervention arm required rescue therapies for refractory hypoxemia. The findings of this study suggest that $P_{L,end\text{-}exp}$-guided PEEP titration may be necessary only in a fraction of patients in whom PEEP titration is more challenging, like those with abnormal chest wall compliance. Indeed, a more recent study [12] in obese patients with acute respiratory failure showed that PEEP titration to target a positive $P_{L,end\text{-}exp}$ was associated with higher end-expiratory lung volume, and improved lung compliance and oxygenation compared to baseline PEEP setting.

34.3.2 Monitoring $P_{L,end\text{-}insp}$ and ΔP_L for Tidal Volume/Inspiratory Pressure Titration to Prevent Overdistention

The cornerstone of lung protective ventilation is low tidal volume, which, as many studies have shown, reduces mortality by minimizing lung overdistention [10, 11]. Indices of potential tidal overdistention include high Ppl (>30 cmH_2O) and ΔP (>15 cmH_2O) [10, 11, 15]. Nonetheless, lung injury is mediated by high $P_{L,end\text{-}insp}$ and ΔP_L, and, in patients with high chest wall elastance a high ΔP may not

necessarily correspond to injurious high $P_{L,end\text{-}insp}$, and ΔP_L. One study in ARDS patients [16], showed a linear correlation between ΔP and ΔP_L, but with a correlation coefficient of 0.7, and about a third of patients with an $\Delta P > 15$ cmH_2O had a $\Delta P_L < 11$ cmH_2O. Moreover, in ARDS patients, the E_L to E_{RS} ratio ranges between 0.2 and 0.8, corresponding to ΔP_L between 3 and 12 cmH_2O for a ΔP of 15 cmH_2O ($\Delta P_L = \Delta P * E_L/E_{RS}$, Fig. 34.2) [17].

The effects of ventilation targeting specific thresholds for $P_{L,end\text{-}insp}$ and ΔP_L have not been tested in clinical studies. A 'safe' threshold for $P_{L,end\text{-}insp}$ of 25 cmH_2O was implemented in the study of Pes-guided protocol for PEEP titration [13], but was never actually observed. A threshold of $\Delta P_L < 20$ cmH_2O is proposed for patients with healthy lungs, and of 10–12 cmH_2O for those with ARDS [10, 11]. The rationale for these proposed thresholds is based on several physiological and experimental observations. First, from the static pressure-volume curve of the lungs, we know that, at TLC, $P_{L,end\text{-}insp}$ is normally approximately 30 cmH_2O, and above 20 cmH_2O the slope of the curve decreases. Second, experimental data indicate that lung injury can occur in healthy lungs when the strain (ΔV/FRC) induced by the ventilation is greater than 1.5–2 [18]. The proportionality constant (k) between stress (ΔP_L), and strain is 12–13 cmH_2O, so injurious strain can be imposed in healthy lungs when stress (ΔP_L) is 18–26 cmH_2O. For ARDS patients lower strain thresholds are proposed, because, due to lung inhomogeneity, regional stress can be double than the global [19]. Additionally, the validated threshold of ΔP (15 cmH_2O), corresponds to a ΔP_L of 10 cmH_2O, based on the observation that the E_L/E_{RS} is usually 0.7 [17].

Injurious high P_L may also occur during assisted ventilation. As early assisted breathing is desirable to avoid diaphragmatic atrophy, the need to monitor for injurious $\Delta P/\Delta P_L$ is increasing. In spontaneously breathing patients, passive conditions to measure driving pressure cannot be reliably obtained [20], so when a high ΔP is measured with an inspiratory hold, direct measurement of ΔP_L could provide a more accurate estimation of lung stress.

34.3.3 Monitoring Spontaneous Effort to Prevent Over- and Under-Assist and Optimize Patient-Ventilator Interaction

A diaphragm-protective ventilation strategy requires active diaphragmatic contractions avoiding both excessively high and low effort, and matching of the mechanical and neural inspiratory time to prevent eccentric diaphragm contractions, although specific protocols and thresholds have not been tested yet in clinical studies.

During normal quiet breathing the range of PTP and WOB is 80 ± 20 $cmH_2O*s*min^{-1}$ and 0.35 ± 0.1 J/L, respectively [21]. Several studies [21–23] suggest that successful weaning is associated with breathing effort up to double of normal range (PTP < 200 $cmH_2O*s*min^{-1}$ and WOB < 1 J/L). A simpler tool to monitor inspiratory effort at the bedside is the swing of Pes or Pdi during tidal

breathing. The range of Pes and Pdi swings during resting breathing is 7 ± 3 cmH_2O [21]. Two recent studies [24, 25] have described the correlation between Pes/Pdi swings and effort, as indicated by PTP or WOB, and Pes swings greater than 14–18 were found associated with increased effort (PTP > 150–200 $cmH_2O*s*min^{-1}$) [24].

Avoiding excessively low inspiratory effort is extremely important, as patients during assisted ventilation are at risk for over-assist and diaphragm atrophy [10, 11]. Titrating assist to a PTP greater than 40–50 $cmH_2O*s*min^{-1}$ has been suggested [10, 11]. Based on currently available data, patient effort monitored by Pes swings, could be titrated to a relatively broader-than-normal range, between 5 and 15 cmH_2O [10, 11, 24].

Monitoring of Pes allows identification of patient-ventilator asynchronies more clearly and accurately than inspection of the pressure and flow waveforms (Fig. 34.4). Triggering delay, is defined as the time from the beginning of the patient's effort to the beginning of ventilator pressurization [26], and can be quantified from Pes. Triggering delay is determined by the ventilator's characteristics, but also influenced by the patient's effort, and long delays can be observed in patients with weak efforts [27]. Auto-triggering is another form of asynchrony often difficult to differentiate from weak inspiratory efforts without monitoring of Pes [26].

Ineffective efforts are the most common asynchronies, and are associated with worse patient outcomes [28]. Ineffective efforts can occur when a patient's effort is not adequate to trigger the ventilator, either because the effort is low, or because there is intrinsic PEEP. Although inspection of pressure/flow waveforms can help identify ineffective efforts, monitoring of Pes and Pdi can provide accurate quantification of inspiratory effort and PEEPi (Figs. 34.3 and 34.4).

Entrainment or reverse triggering refers to diaphragmatic contractions occurring as a result of the mechanical breath [29]. In patients with injured lungs, entrainment can cause lung overstretch by breath-stacking (delivery of double volume) or regional overstretch by pendelluft phenomenon (volume shift from the nondependent to the dependent lung regions during a breath) [4]. Entrainment is characterized by a stable time-difference between the onset of the mechanical and the neural breath, which can be calculated from the Pes waveform (Fig. 34.4). Lack of inspiratory efforts during an expiratory hold or a CPAP trial can discriminate reverse triggering from spontaneous efforts.

Monitoring of Pes allows accurate evaluation of neural inspiratory time, and helps identify and correct asynchronies related to the duration of the pressurization phase, the delayed and premature cycling-off [26]. Matching of the mechanical to the neural inspiratory time can be easily performed at the bedside by adjusting the cycling-off criterion, when the neural inspiratory time can be directly visualized in the Pes tracing. Avoiding such asynchronies is important for protective ventilation [11], as premature cycling-off, with or without double triggering, may promote both lung and diaphragm injury, by increasing lung stress, and subjecting the diaphragm to eccentric contractions, while delayed cycling-off is associated with over-assist and may promote the development of PEEPi and ineffective efforts.

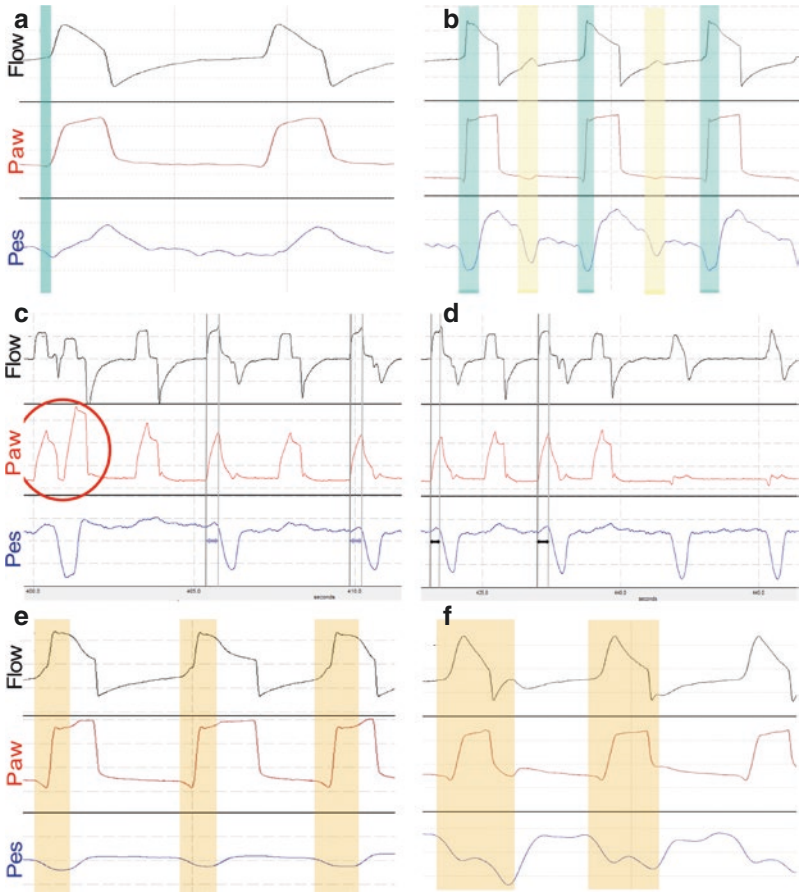


Fig. 34.4 Recognition of asynchronies. From top to bottom, flow, airway pressure (Paw), and esophageal pressure (Pes) tracings over time. (**a**) Triggering delay and auto-triggering: in pressure support mode a small patient's effort triggers the first breath, followed by relaxation of inspiratory muscles, indicated by the upward shift of Pes, (like in passive ventilation). The triggering delay (highlighted blue) is 120 ms, and, in this case, is almost as long as the patient's effort. The second breath is an auto-triggered breath, as no effort can be detected in the Pes waveform. This auto-triggering is not visible in the Paw waveform. (**b**) Ineffective efforts in high level of pressure support: patient's effort can be identified on the Pes waveform tracing, the first, third, and fifth trigger a ventilator delivered breath (highlighted blue) while the second and fourth are ineffective (highlighted yellow). A small distortion in expiratory flow indicates the presence of ineffective effort, but the Pes waveform can help identify the patient's effort more clearly. (**c**) Breath-stacking and entrainment (reverse triggering) in assist volume control: an effort extending in mechanical expiratory time triggers the delivery of a second, stacked breath, increasing tidal stress (red circle). Such a patient's effort can occur as a result of entrainment, characterized by a stable temporal relationship with the mechanical breath (purple arrows) and can be measured using the Pes waveform. (**d**) Spontaneous efforts in a control mode can mimic entrainment, and can be discriminated from the lack of stable temporal relationship with the mechanical breath (black arrows) and the presence of efforts during a CPAP trial. (**e**, **f**) Mismatch of mechanical and neural inspiratory time: in pressure support mode the neural inspiratory time (highlighted orange) can be shorter than the mechanical cycle, characterized as delayed cycling-off (**e**), or longer than the mechanical cycle, characterized as premature cycling-off (**f**)

34.4 Conclusion

In conclusion, Pes monitoring is a valuable tool, easily applicable at the bedside, which helps provide individualized, protective ventilation. Better monitoring devices with smart alarms, and larger clinical studies are expected in the future to translate the physiological rationale of individualized ventilation into documented patient benefit.

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Lung Volumes and Volumetric Capnography

35

Hong-liang Li, Jian-Xin Zhou, and Lu Chen

35.1 Introduction

Mechanical ventilation is lifesaving but can also generate secondary injury and inflammation, termed ventilator-induced lung injury (VILI). Assessment of lung volumes is essential for understanding respiratory mechanics of each individual patient to reduce the risk of VILI [1]. While tidal volume (V_T) is routinely monitored, other volumes, such as end-expiratory lung volume (EELV) and recruited volume, deserve more attention for providing safer ventilation [2–4]. On the other hand, measurement of dead space is fundamental for evaluating gas exchange to optimize ventilator settings. Volumetric capnography provides a noninvasive and continuous approach for monitoring dead space and effectiveness of ventilation at the bedside. In this chapter, we will address some relevant questions regarding lung volumes and volumetric capnography.

H.-l. Li · J.-X. Zhou
Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

L. Chen (✉)
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Keenan Research Centre, Department of Critical Care, St Michael's Hospital, Toronto, ON, Canada
e-mail: lu.chen@unityhealth.to

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35.2 Lung Volumes

35.2.1 Why Is Measuring Absolute Lung Volume Clinically Relevant?

Measuring absolute lung volumes is physiologically important for lung protective ventilation, though it is not widely performed in routine practice yet. For example, a key characteristic of acute respiratory distress syndrome (ARDS) is the reduction in functional residual capacity due to atelectasis and consolidation. In patients receiving positive end-expiratory pressure (PEEP), the functional lung volume can be defined as the sum of functional residual capacity and the recruited volume induced by PEEP. This reflects how much lung can receive V_T. Assessing the functional lung volume allows for the calculation of lung strain (V_T over functional lung volume), which indicates lung deformation related its original status. Experimental studies have shown that strain is a key determinator of VILI. Clinical trials also support this finding since a surrogate of strain (i.e., driving pressure) presented the strongest association with survival rates among all the respiratory mechanics parameters evaluated.

35.2.2 How Are Absolute Lung Volumes Measured?

There are three main methods for measuring the absolute lung volumes: (1) The most sensitive approach is, likely, the quantitative analysis of computed tomography (CT) scans, which also shows the regional distribution of lung volume. It is based on the linear correlation between the X-ray attenuation in a voxel and the physical density of that voxel. For example, a density of −500 Hounsfield unit (HU) with suggests that the voxel is composed half by tissue (with a radiodensity equivalent to water) and half by gas. In other words, it is possible to calculate the amount of gas and tissue for any given voxel (and thus any lung region) from its CT number. The CT scan, however, is also the most complex and time-consuming method. (2) Gas dilution technique, which estimates lung volume based on the gas-diluted concentration during equilibration for an inert gas (e.g., helium). This technique is usually used in a pulmonary function test laboratory and is overcomplicated for implementing in ICUs. (3) Olegard and colleagues proposed a modified nitrogen washout/in technique, which is based on a step change in FiO_2. This technique allows to measure EELV without interruption of mechanical ventilation and is available in a specific commercial ventilator.

35.2.3 How Are the Changes in Lung Volume Measured?

The most common assessment for changes in lung volume is V_T, which is calculated as the integration of flow with respect to time. A flow sensor is therefore necessary for the assessment of V_T. A modern ventilator is typically equipped with an

inspiratory sensor and an expiratory flow sensor embodied in the machine (distal from the patient). A reliable measurement of expiratory V_T requires assessing the leak rate in the tubing and compliance of the ventilator circuit. Some ventilators are also equipped with a proximal flow sensor placed between the Y-piece and the endotracheal tube, providing better accuracy. Though its accuracy is reduced by water vapor and secretions, a proximal flow sensor is particularly useful for pediatric patients [5]. Due to the inevitable drift in flow signals, all ventilators reset V_T to zero at the beginning of a newly detected breath. This technical manipulation leads to remarkable underestimation of volume delivered to the patient when breath stacking occurs. For example, a patient might be ventilated at a 6 ml/kg of V_T during regular breaths in volume control mode, but when breath stacking presents due to reverse triggering, the actual V_T could rise to as much as 12 ml/kg. This issue should be noted during clinical practice to provide better lung protective ventilation.

V_T measured by flow sensors allows to calibrate the tidal changes in impendence measured by Electrical Impedance Tomography (EIT). For instance, regional compliance of the respiratory system can be calculated by using the reginal V_T over driving pressure. Through EIT, Yoshida et al. [6] demonstrated the pendelluft phenomenon of V_T distribution and highlighted the potential overstretching in the dependent lung regions during spontaneous breathing: this cannot be detected by monitoring the "global" V_T.

Another important change in lung volume is the one induced by PEEP. PEEP-induced lung volume changes involve two elements: the inflation/hyperinflation of the already opened lung units and the recruitment of the collapsed lung units [7, 8]. We will introduce their measurements in the sections below.

35.2.4 How Is Recruitment Measured Using Computed Tomography?

The most intuitive approach for assessing lung recruitment is the thoracic CT, early described by Gattinoni et al. [9]. As mentioned in the previous section, CT scans can be used to assess EELV. The change in EELV is thus the difference in EELV between two PEEP levels. Moreover, the regional aeration of lung tissues can be measured and categorized through a CT-scan. Non-aerated tissue is defined as lung tissue with CT numbers between −100 and 100 HU; poorly aerated tissue is the tissue between −500 and −101 HU; well-aerated tissue is the tissue between −900 and −501 HU; and hyperinflated tissue is the tissue between −1000 and −910 HU [1]. The change in EELV can then be divided into recruitment, inflation, and hyperinflation based on the changes in regional aeration levels. However, the concrete definition of recruitment is debated. There are two approaches for defining recruitment through a CT scan: Gattinoni's approach [2] and Rouby's approach [10]. We summarized their major differences, which are important for practice, in Table 35.1. During the last three decades, CT scan has greatly advanced our understanding in recruitment generated by PEEP and by prone positioning [2, 11]. Despite its usefulness, CT scan are rarely used for assessing recruitment during clinical practice, likely due to the

Table 35.1 Differences between Gattinoni's approach and Rouby's approach for assessing recruitment using CT-scan

	Gattinoni's approach	Rouby's approach
Comparison	Voxel based	Anatomical regions based
Lung tissues	Non aerated	Non and poorly aerated
Threshold	−100 HU	−500 HU
Calculation	Change in tissue weight[a]	Change in gas volume
Analogy	Like an independent *t*-test in statistics, lung regions at high PEEP are not paired with the regions at low PEEP for comparisons	Like a paired t-test in statistics, lung regions at high PEEP are paired with the regions at low PEEP for comparisons

[a]Tissue weight is obtained from tissue volume, assuming the tissue density is 1 g/ml

increases in both radiation and transportation risks and how time consuming it is for quantitative analysis.

35.2.5 How Is Recruitment Measured Using Pressure–Volume Curves?

Compared with the morphological approach (i.e., CT scans), a mechanic-based approach using multiple pressure–volume curves is less intuitive (no direct visualization of lung recruitment) but more feasible for bedside assessment. The rationale of the pressure–volume curves approach is to measure the recruited or de-recruited volume as the volume difference between two pressure–volume curves for a given static pressure. Note that these two pressure–volume curves are generated from two PEEP levels (Fig. 35.1) and hence start from different EELV. In order to plot these on the same axes, to allow comparisons, the EELVs should be measured using techniques mentioned in the previous section (e.g., nitrogen washout/in technique). Furthermore static (elastic) pressure can be measured by using slow-flow (i.e., 5 L/min) inflation, where resistive pressure is neglectable. If a remarkable recruitment is generated by higher PEEP, there would be a large volume shift between pressure–volume curves for the same elastic pressure (Fig. 35.1a). Contrastingly, if a recruitment is minimal, the volume difference would be small (Fig. 35.1b). The pressure–volume curves, though easier than the CT scan approach, is still cumbersome for routine practice.

35.2.6 How Is the Recruitment-to-Inflation Ratio Measured?

In a recent clinical study, Chen et al. [8] proposed a single-breath maneuver to measure lung recruitment at the bedside (Fig. 35.2). The rationale of this maneuver was derived from the multiple pressure–volume curves. It only requires reducing PEEP for a few breaths, which takes less than 1 min to be done at the bedside. The authors

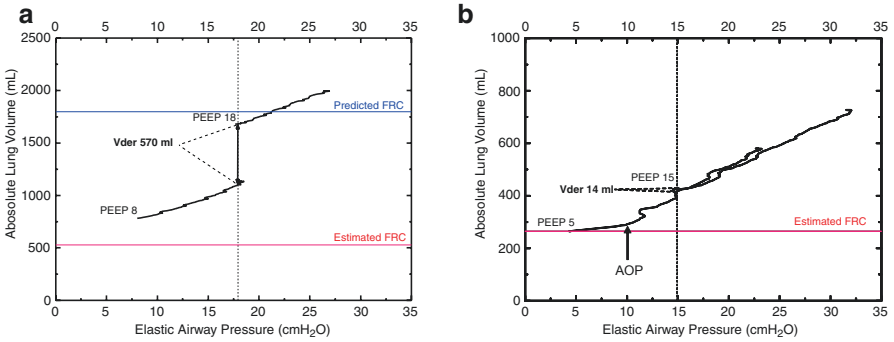

Fig. 35.1 Assessment of de-recruited volume through multiple pressure–volume curves. Panel (**a**) is a representative patient with high recruitability whereas Panel (**b**) is a patient with low recruitability and airway closure. Absolute lung volume is measured by nitrogen washout/in technique. Elastic airway pressure is measured by slow-flow (5 L/min) inflation. Vder is the derecruited volume assessed as the volume difference between two pressure–volume curves at a same elastic pressure (at 18 cm H_2O in panel **a**; at 15 cm H_2O at panel **b**). AOP is airway opening pressure in a patient with complete airway closure [25]. Estimated functional residual capacity (FRC) is estimated by withdrawing PEEP and subtracting the exhaled PEEP-induced lung volume from the end-expiratory lung volume at a PEEP level. Predicted FRC at supine position is predicted based on gender and height

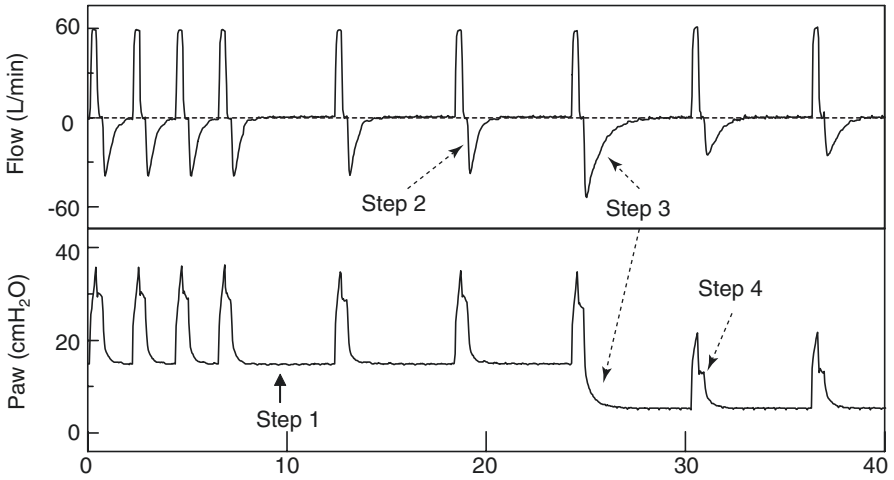

Fig. 35.2 Measurement of the recruitment-to-inflation ratio through a single-breath maneuver. Steps of measurement: (1) reduce respiratory rate to 6–8 breaths per minute to allow minimizing auto PEEP; (2) after one or two breaths, document the exhaled tidal volume (V_T) at high PEEP; (3) reduce PEEP by 10 cm H_2O (e.g., from 15 to 5 cm H_2O) and document V_T the exhaled from high to low PEEP; (4) document the plateau pressure (Pplat) at low PEEP and resume previous ventilator setting. The documented data can then be entered into an online calculator at https://crec.coemv.ca (video demonstration is also available)

also emphasized that the benefit of recruitment in closed lung units should be balanced by the price of inflation/hyperinflation in already opened lung units, and proposed an index called the recruitment-to-inflation (R/I) ratio [8]. The R/I ratio can be used as a continuous variable for assess the potential recruitment related to inflation (the high R/I, the greater potential), and can also be discretized for determining lung recruitability (R/I $\geq$ 0.5 suggests highly recruitable; R/I < 0.5 suggests poorly recruitable). Thanks to the simplicity for measuring the R/I ratio, it can be used in even very constrained environments such as in patients with COVID-19-induced ARDS [12].

35.3 Volumetric Capnography

35.3.1 What Is Dead Space?

Dead space is the part of tidal volume that does not participate in gas exchange. Pure dead space denotes the ventilated lung units without perfusion; in other words, lung areas with infinite ventilation to perfusion ratio (V/Q). It is, however, impractical to differentiate pure dead space from the lung units with high V/Q ($1 < V/Q < \infty$) during clinical practice. Both pure dead space and high V/Q present similar effects on carbon dioxide (CO_2) elimination, and therefore, they are considered to be the same. Physiological dead space (VDphys) involves two components: (1) conducting airways (VDaw) and (2) ventilated alveoli with poor or no perfusion (VDalv). In a mechanically ventilated patient, there is an additional dead space generated by instruments between endotracheal tube and the Y-piece of circuit, such as heat and moisture exchanger, bacterial-viral filters, and connectors, which should be minimized as much as possible. In this chapter, we will consider the instrumental dead space as a part of VDaw unless specified.

35.3.2 How Is Dead Space Calculated?

Dead space is commonly presented as an absolute volume of one single breath, which can be calculated using Bohr's formula proposed in 1891, or its rearrangement:

$$VD_{phys} = \frac{P_{\bar{A}}CO_2 - P_{\bar{E}}CO_2}{P_{\bar{A}}CO_2} \times V_T$$

where $P_{\bar{A}}CO_2$ is the average partial pressure of CO_2 in alveolar gas, $P_{\bar{E}}CO_2$ is the average partial pressure of CO_2 in mixed exhaled gas, and V_T is the tidal volume. It is worth noting that Enghoff modified Bohr's formula, which replaces $P_{\bar{A}}CO_2$ with the partial pressure of CO_2 in arterial blood, should be considered as an index of global V/Q mismatching rather than dead space [13, 14]. Indeed, Enghoff's approach provides information from both sides of the alveolar-capillary membrane and thus

involves both dead space and intrapulmonary shunt [13–15]. The requirement of arterial blood samples also precludes the Enghoff's approach from noninvasive, real-time monitoring. We therefore recommend using the original Bohr's approach for calculating dead space.

35.3.3 What Is Capnography?

Capnography refers to the graphical display of the concentration or partial pressure of CO_2 against time or volume. Time-based capnography is mainly used for monitoring the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) during clinical practice. Note that $P_{ET}CO_2$ is not equivalent to $P_{\bar{A}}CO_2$ (required for calculating dead space) even if a plateau partial pressure of CO_2 during expiration is observed. Volume-based, or the volumetric, capnography merges CO_2 and volume signals for plotting concentration or partial pressure of CO_2 over exhaled tidal volume. Unlike time-based capnography, volumetric capnography provides all the information required for calculating dead space.

35.3.4 What Is a Capnometer?

A capnometer is a noninvasive device measuring the concentration of CO_2 in exhaled gas. It is based on the feature that CO_2 preferentially absorbs infrared radiation at a specific wavelength (4.26 μm). There are two types of capnometer depending on the site of sensor. Mainstream capnometers use an infrared sensor at a sampling site located between the endotracheal tube and the Y-piece. Side-stream capnometers transport exhaled gas from the sampling site to a distal sensor through a sampling tubing. Side-stream capnometers are widely used in operating room and intensive care unit, probably because it is disposable and easy for monitoring $P_{ET}CO_2$. However, there is a delay between the flow and CO_2 concentration signal, which even if corrected might induce some distortion in the shape of volumetric capnography [16]. A mainstream capnometer provides rapid and accurate analysis of CO_2 concentration, synchronized with the main flow and it is hence preferable for measuring dead space.

35.3.5 How Is Dead Space Measured Using Volumetric Capnography?

As illustrated in Fig. 35.3, volumetric capnography can be divided into three phases: phase I is the CO_2-free gas from airways and instruments (if the instruments are added between the CO_2 sensor and the patient); phase II represents the transition between the airways and the alveoli; phase III is pure alveolar gas. Phases II and III are separated by the intersecting point of the lines following the slope of phases II and III, respectively. The inflection point (i.e., the point at which the curvature of a

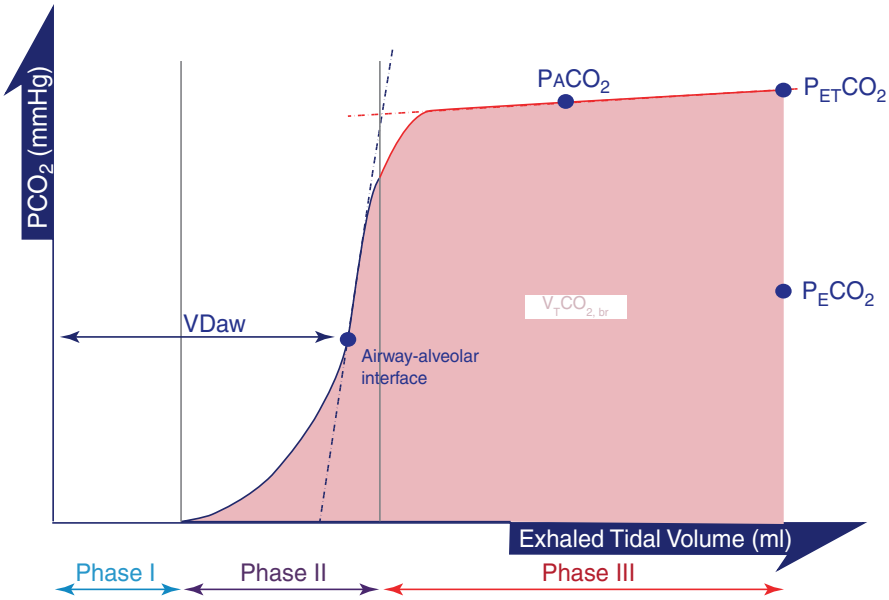

Fig. 35.3 Illustration of measuring dead space by volumetric capnography. PCO_2 is partial pressure of carbon dioxide. $P_{\bar{A}}CO_2$ is the average partial pressure of CO_2 in alveolar gas, $P_{\bar{E}}CO_2$ is the average partial pressure of CO_2 in mixed exhaled gas. $P_{ET}CO_2$ is the end-tidal partial pressure of CO_2. $V_TCO_{2,\,br}$ is the amount of CO_2 eliminated by a tidal breath (area under the curve). VDaw is the volume of airway dead space

curve changes) of phase II is deemed to be a mark of airway–alveolar interface using Fowler's concept [17]. The volume exhaled from the beginning of expiration to this point is then the VDaw. The area under of the CO_2–volume curve represents the amount of CO_2 eliminated by a tidal breath ($V_TCO_{2,\,br}$), which can be calculated from numerical integration. $P_{\bar{E}}CO_2$ can be then calculated by multiplying $V_TCO_{2,\,br}$ to V_T fraction by the barometric pressure. In the past, the most challenging part of the calculation of dead space was measuring the $P_{\bar{A}}CO_2$. Thanks to Fletcher and Jonson's theoretical work [14] and Tusman's validation [18], we can now directly determine $P_{\bar{A}}CO_2$ by the midpoint between the airway–alveolar interface and $P_{ET}CO_2$ following the slope of phase III. VDphys can then be calculated by plugging the values of $P_{\bar{A}}CO_2$ and $P_{\bar{E}}CO_2$ into Bohr's formula. Knowing the values for both VDphys and VDaw, we can eventually calculate alveolar dead space as

$$VD_{alv} = VD_{phys} - VD_{aw}$$

Clearly, the above process of measurements requires computer assistance; in fact, most studies used a customized research software. A commercially available software integrated with ventilators, which can automatically complete all these measurements of dead space, may facilitate the implementation of volumetric capnography at the bedside.

35.3.6 What Are the Clinical Implications?

By measuring dead space and other volumetric parameters, volumetric capnography provides a wide range of potential clinical applications in mechanically ventilated patients [19]. For example, several clinical studies have demonstrated that elevated VDphys was strongly associated with mortality in both early and late ARDS, in moderate and severe ARDS, from different etiologies [20, 21]. Indeed, VDphys presented a stronger association with the outcome than any oxygenation derived indices, highlighting the prognostic value of dead space. Volumetric capnography can be used for personalizing ventilator settings. Perhaps the most obvious application is used for optimizing V_T. Among different volumetric capnography derived parameters, Jonson proposed an efficiency index which can directly indicate ventilatory efficiency with respect to CO_2 elimination [22]. Moreover, the measurement of dead space can help assess alveolar recruitment and overdistension, providing useful information for PEEP titration [23]. It can also be used to assess fluid responsiveness and estimate cardiac output noninvasively [24]. These applications, though promising, require further extensive clinical study to be validated.

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Radiological Monitoring

36

Jean-Michel Constantin, Elodie Baron, and Bao Long Nguyen

36.1 Introduction

The prescription of lung imaging in the ICU is a controversial topic, always relevant but not always rational. Although the use of bedside chest radiography (CRX) is almost as old as critical care, its use has been largely challenged by the advent of ultrasound. Also lung CT scan, which remains the gold standard for assessing lung morphology and acute or chronic lung injury, has been challenged by noninvasive techniques such as ultrasound and EIT conventional [1]. Historically, ICU physicians assumed that daily CXRs were important for assessing the progression of lung disease and monitoring the status of commonly used indwelling devices (i.e., central venous catheters, nasogastric tubes, pulmonary artery catheters, endotracheal tubes, etc.). Since more than a decade, the scientific literature has shown that routine daily CXR increases the cost of care, does not change clinical practice and should no longer be recommended [2]. In addition to this evidence base, much of the historical rationale for routine daily CXRs may no longer exist in contemporary critical care clinical practice. For example, modern ventilators closely monitor pulmonary mechanics (plateau pressure, compliance, and resistance) while noninvasive sensors can monitor CO_2 and oxygen levels to guide clinical management. More importantly, point-of-care lung ultrasound has become widely available and may outperform CXR in the diagnosis of certain acute lung conditions such as pneumothorax [3]. But what trials comparing routine and on-demand CRX have shown is that the reduction in CXR use in these trials was due to a decrease in morning systematic

J.-M. Constantin (✉) · E. Baron · B. L. Nguyen
Sorbonne University, GRC29, AP–HP, DMU DREAM and Department of Anesthesiology and Critical Care, Pitie-Salpetriere Hospital, Paris, France
e-mail: jean-michel.constantin@aphp.fr

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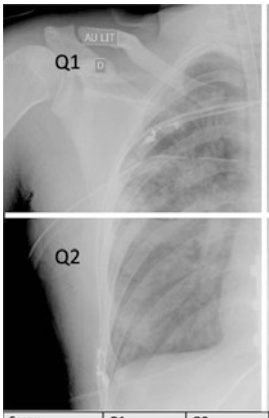
CXR, with no difference in unplanned CXR [4]. This does not mean that CXR lacks of value, it rather means that routine CXR should be avoided because of its low added value. What can we expect from an imaging technique at what point in the disease? These should be the questions to ask before requesting lung imaging in the ICU. We will try to give an overview of these conditions.

36.2 What Could We Expect from Chest X Ray in ICU?

36.2.1 Assessing Lung Oedema

Pulmonary edema is a frequent cause of ICU admission, and it also represents a frequent complication that occurs during an ICU stay. Two types of pulmonary edema can be differentiated, based on the underlying pathophysiology: the hydrostatic edema, due to congestive heart failure or fluid overload; and an increased-permeability edema leading to acute respiratory distress syndrome (ARDS). Classic findings in congestive heart failure include widening of the vascular pedicle and vascular congestion with peri-bronchial cuffing, dilated and unsharp vascular structures, and thickening of the interlobular septa (Kerley B lines) that progresses to a so-called "bat-wing" alveolar edema with bi-hilar consolidations. In addition, cardiomegaly and bilateral pleural effusions are typical findings in congestive heart failure [5]. A variety of pulmonary and extrapulmonary diseases may cause increased permeability of the capillary wall, leading to noncardiogenic pulmonary edema. Radiographically, the distinction between hydrostatic and increased-permeability pulmonary edema can often be challenging. The clinical presentation, data from cardiac ultrasound, the distribution of the opacities, and the course are important factors for narrowing the differential diagnosis and for distinguishing cardiologic pulmonary edema from pneumonia or ARDS. In addition, interstitial pneumonia or pulmonary hemorrhage can demonstrate identical radiographic findings that are indistinguishable from interstitial pulmonary edema. In these cases, only CT scan can be diagnostic.

CXR may be of greater interest in assessing the amount of pulmonary edema and changes in pulmonary edema related to time or therapeutic interventions in ARDS. The Radiographic Assessment of Lung Edema (RALE) score has been proposed as a noninvasive tool to assess the radiographic extent of pulmonary edema in patients with ARDS (Fig. 36.1) [6]. The RALE score provides a semiquantitative measure of the extent and density of alveolar opacities on chest radiography that correlates well with the degree of pulmonary edema assessed by gravimetric measurements in explanted human donor lungs. When calculated from enrollment CXR of patients enrolled in the ARDSNet Fluid and Catheter Treatment Trial (FACTT), the RALE score was associated with both the severity and clinical outcomes of ARDS. Changes in RALE score during the first days after the onset of ARDS is independently associated with survival in a retrospective analysis of a randomized controlled trial. It may therefore be useful at the bedside or as a surrogate endpoint in ARDS clinical trials [7].



Score	Q1	Q2	Q3	Q4	Total
Consolidation	4	4	4	4	
Density	1	2	3	3	
Quadrant Score	4	8	12	12	36

CONSOLIDATION	
Consolidation Score	Extent of alveolar opacities
0	None
1	<25%
2	25-50%
3	50-75%
4	>75%
DENSITY	
Density Score	Density of alveolar opacities
1	Hazy
2	Moderate
3	Dense
FINAL RALE SCORE	
Right Lung	Left Lung
Upper quadrant Cons x Den = Q1 score	Upper quadrant Cons x Den = Q3 score
Lower Quadrant Cons x Den = Q2 score	Lower Quadrant Cons x Den = Q4 score
Total RALE= Q1+Q2+Q3+Q4	

Fig. 36.1 RALE score definition and example calculation of RALE score of an ARDS patient

36.2.2 Positioning of Monitor and/or Therapeutics Devices

- Central Venous Lines: Ideally, the tip of a central venous catheter is located just above the right atrium in the distal superior vena cava. Malposition is seen in about 10% of controls. The most frequent complication is a pneumothorax in about 6% of patients and is more common with the subclavian than the internal jugular approach [8]. Notwithstanding, CXR is not the more accurate tool for assessing pneumothorax and an initial normal CXR do not excludes a late pneumothorax. A late-appearing pneumothorax should be suspected in patients with respiratory deterioration hours or days after line placement.
- Chest Tube: The optimal positioning of a chest tube depends on its indication, whether it is used to evacuate a pneumothorax or a pleural effusion, and on the extent and location of the air or fluid accumulation. The side holes of the chest tube should project within the pleural space. Even if lung ultrasound may be use, to assess pleural effusion volume and/or regional anatomy, CXR remains indicated after insertion to control the position of the tube, to evaluate the efficacy of the drainage, and to rule out associated complications [8]. Malposition of a chest tube includes locations in the interlobar fissure, lung parenchyma, the chest wall, or even the abdomen.
- Nasogastric Tube: The optimal position of the nasogastric tube depends on its intended use; if it is used for feeding, its tip should be in the stomach cavity or distal to it (post-pyloric) to reduce the risk of aspiration. All side ports, which are several centimeters from the tip of the tube, should be placed in the stomach to avoid aspiration. Nasogastric tube malposition is rare, but potentially fatal if clinically unsuspected. After insertion of a nasogastric tube, a CXR is strongly recommended to confirm the correct position of the tube, at least before infus-

ing enteral nutrition. The most common malposition of the nasogastric tube is when it loops in the oropharynx, esophagus, or stomach, with the tip positioned upward.
- CXR may be used for all other devices, as pulmonary artery catheters, aortic balloon, tracheal tubes, etc. The benefit of a CXR instead of ultrasound must be assessed carefully depending of the patient and the team expertise.

36.2.3 Pleural Effusions

Pleural effusion is very common in ventilated ICU patients (more than 60%). It can be transudate, exudate, or blood. The classic imaging findings of a liquid pleural effusion are hazy basal opacification without air bronchogram, obliteration of the diaphragm contour, and blunting of the lateral costophrenic angle. CXR has low sensitivity for detecting pleural effusion, good specificity but is not effective in assessing the volume of fluid in the pleural space. Lung ultrasound is a more effective tool for assessing pleural effusion and the indication for paracentesis and chest drainage. Pneumothorax is seen in trauma patients but can also be iatrogenic after line placement or following barotrauma in ventilated patients [3]. While the diagnosis of a complete pneumothorax is obvious, when it is partial and/or anterior, the sensitivity of CRX drops. Lung ultrasound may be more sensitive, but sometimes only CT scan is able to diagnose pneumothorax.

36.2.4 Pneumonia

Nosocomial pneumonia is a common problem in ICU patients, especially in those who are ventilated and with ARDS [9]. The diagnosis of pneumonia is often difficult, both clinically and radiographically. Airspace opacities of the lung parenchyma are the hallmark of pneumonia, but these may also be present with atelectasis, aspiration, hemorrhage, or pulmonary edema. Typical radiographic features supporting the diagnosis of pneumonia are areas of patchy consolidation or ill-defined opacities, often multifocal, without volume loss in nondependent areas of the chest. Air bronchograms are typical of pneumonia but are not specific. Radiographic changes in opacities over several days are typical of pneumonic infiltration, in contrast to edema, in which opacities change within hours of treatment. The specificity of CXR is low but remains an interesting tool for this difficult diagnosis [3].

36.3 When is CT Scan Indicated in Ventilated Patients?

CT has profoundly changed the understanding of the pathophysiological processes underlying ARDS, and contributed to a better description of the topographic distribution of the loss of gas and tissue excess [10, 11]. CT can both be assessed visually,

as typically done by radiologists, or quantitatively with computer-based analysis. In fact, CT creates an image in which each volume element (voxel) is attributed a value corresponding to its ability to attenuate X-rays, and it is normalized to a standard scale from −1000 to 0 Hounsfield units corresponding to air and water attenuation respectively [12]. Quantitative analysis of CT scan is mostly used for research, to assess recruitability, response to positive end expiratory pressure (PEEP) or postural maneuvers [13]. These methods are time-consuming, require specific software and a high level of expertise. To translate research tools to clinical practice, it would be desirable to standardize and automate analysis through a machine learning algorithm as it has been proposed for other applications, like sarcopenia evaluation with abdominal CT scan [14].

At the early phase of ARDS, in clinical practice, visual evaluation of CT scan allows to assess lung morphology and, additionally, to characterize patients as having focal or non-focal ARDS (Fig. 36.2) [15]. These two phenotypes of ARDS have different responses to PEEP, recruitment maneuvers and prone position [16]. Initially, the "CT scan ARDS study group" established three patterns of loss of aeration distribution: focal (loss of aeration predominating in the dorsal part of the lower lobes), diffuse (loss of aeration and tissue excess in the whole lung, most of time bilateral), and patchy (a diffuse CT scan attenuation with healthy lung areas) [17]. In the last 10 years, however, patients showing a diffuse or patchy loss of aeration have been grouped as having non-focal lung morphology, because response to PEEP and biomarkers of lung epithelial injury are not different between these two patterns, and for simplification [18]. Setting ventilator according to these phenotypes makes sense from a physiological point of view, but failed to decrease mortality in a randomized controlled trial, probably because it is not so easy to classify patients according to lung morphology [19]. This is an argument in favor of a classification based on an automatic algorithm or to assess changes in lung morphology in two different CT scan at two levels of pressure to increase diagnostic performance by physicians.

During the time-course of AR DS, CT scan remains the best tool to assess complications related to mechanical ventilation or progression of the disease. Pneumothorax due to volo/barotrauma, pneumonia, empyema, or lung fibrosis. Lung fibrosis is a major complication of ARDS with a potential dramatic outcome. The diagnosis is challenging between pneumonia and lung fibrosis looking to

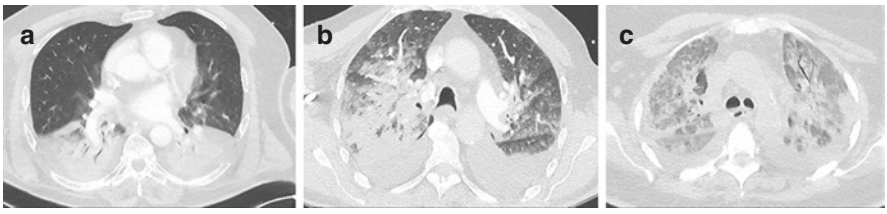


Fig. 36.2 CT scan of three ARDS patients, Focal (**a**) and non-focal (**b**, **c**) with the same PaO_2/FiO_2 of 115 ± 3 mm Hg

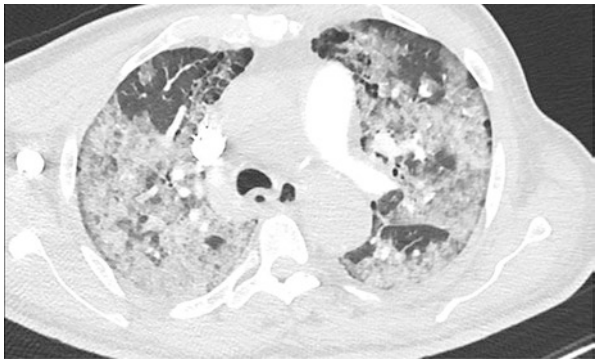


Fig. 36.3 CT scan of a patient with COVID-related ARDS with deteriorating static compliance over 2 days, revealing early pulmonary fibrosis with interlobular septal thickening and traction bronchiectasis

respiratory mechanics or CXR. Unfortunately, therapeutic interventions are lacking. The gold standard for diagnosing ARDS-associated lung fibrosis remains an open lung biopsy and histological examination, which is invasive and cannot be repeated easily, and most of time impossible in hypoxemia ARDS patients. During lung fibrosis, CT scan highlights parenchymal bands, architectural distortion, interlobular septal thickenings, traction bronchiectasis, and sometime honeycombing (Fig. 36.3) [20]. Repeated CT scan when changes in lung physiology are not explicated by natural history of ARDS may be of interest. The benefit-risk balance must be evaluated each time according to the expected relevance of the results obtained, the patient of risk of intra-hospital transport and radiation exposure.

36.4 Conclusions

Monitoring ventilated ICU patients is a daily challenge for ICU teams. Since the advent of pulmonary ultrasound and noninvasive techniques such as EIT, the paradigm has changed. We moved from high cost, routine CXR with low yield, to targeted, on-demand examinations that answer questions posed by physicians. CXR should not be dismissed, as it can still result useful for ventilation monitoring. The CT scan remains the gold standard to evaluate the pulmonary morphology and the complications of the ventilated patient. Clinical reflection supported by the right examination performed at the right time guarantees an efficient monitoring essential to the quality of care in critically ill patients.

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Part V

Educational Material

Teaching Mechanical Ventilation: Online Resources and Simulation

37

Thomas Piraino

37.1 Introduction

The purpose and goals of mechanical ventilation can be described and taught in a variety of written formats. Different modes of mechanical ventilation and the various nuances of their operation can also be described. However, to truly learn the complexities of how mechanical ventilation is applied to a patient, how the individual conditions such as airway resistance, respiratory system compliance, and patient effort impact its application, is something that is best taught through visual means either at the bedside or during simulation. The following chapter will provide resources for learning and teaching mechanical ventilation.

37.2 Online Resources and Applications

The following online resources use various methods to teach concepts of mechanical ventilation but are not tools used for simulation. They include applications, blogs, and online courses with a primary focus of mechanical ventilation.

37.2.1 Standardized Education for Ventilatory Assistance (SEVA)

The Pulmonary and Critical Care Fellowship training program at Cleveland Clinic has developed a standardized system to teach basic mechanical ventilation. The program is called SEVA (Standardized Education for Ventilatory Assistance). It

T. Piraino (✉)
Department of Anesthesia, Division of Critical Care, McMaster University, Hamilton, ON, Canada

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begins with an introductory course and builds up to a master class. All of these courses are free, and can be accessed here https://mylearning.ccf.org/login/index.php (last accessed February 2022).

37.2.2 iVentilate App

The iVentilate app by the SimVA Medical group combines screenshots, videos, case examples and more to help healthcare professionals improve their understanding of mechanical ventilation. It links to studies relevant to each topic and includes various calculators used for bedside assessments. iVentilate is available for free in the AppStore (Apple, Cupertino, CA, USA), and Google Play Store (Google, Mountain View, CA, USA). More information can be found at https://www.sim-va.com (last accessed February 2022).

37.2.3 The Toronto Centre of Excellence in Mechanical Ventilation (CoEMV Blog)

The CoEMV blog is an online blog that publishes articles, interviews, and editorials related to new concepts in mechanical ventilation monitoring, recognition and classification of patient-ventilator asynchronies. It is free to view and subscribe to email updates. http://coemv.ca (last accessed February 2022).

37.3 Mechanical Ventilation Simulation

One of the most useful tools one can use for teaching mechanical ventilation are ventilator waveform screenshots, accompanied by a description of the case to describe what is seen. Many ventilator manufacturers have included screenshot tools which allow the screen to be captured and exported as an image. The limitation of screenshots and video recordings are simply that they are retrospective examples and do not allow the learner to manipulate parameters themselves to see how this would affect the patient–ventilator interaction and its impact on the waveform graphics. For this reason, simulation tools have become the preferred method for in-depth teaching of mechanical ventilation. Various simulation methods exist, and the cost for these methods can vary greatly. Simple software including applications, excel sheets, and websites that do not require a ventilator or dedicated equipment other than a computer or tablet can be used to teach basic up to complex scenarios depending on their features.

37.3.1 Software Simulation Options

37.3.1.1 Simulation Interface for Ventilation Analysis (SIVA)

An advanced script was developed by Robert L. Chatburn, MHHS, RRT-NPS, FAARC using Microsoft Excel, and has been widely distributed among educators (Fig. 37.1). It has the three most widely used modes to choose from; Volume Control (VC-CMV), Pressure Control (PC-CMV), and Pressure Support (PC-CSV), and all settings related to ventilation can be adjusted, and the changes are shown visually in graphic form. In addition, patient variables such as resistance, compliance, and patient effort can be altered to visualize their impact on the ventilator waveform. What makes this simulation file unique is the patient effort is highly customizable with strength of the effort (Pmus), length of the effort, and even a delay in effort for demonstrating the visual impact of asynchronies such as reverse triggering and ineffective efforts, short-cycling and delayed cycling. In addition to simulated graphics, the file has many more resources such as equations, example of mode classifications, and a comparison of ventilator modes between commercially available mechanical ventilators. The file can be downloaded from this link https://1drv.ms/x/s!AuFakBJODC3Dgtlhw03JXi8I2dzTTA?e=6u86gP (last accessed February 2022).

37.3.1.2 VentSim

VentSim is an online interactive simulation website created by Dr. Sami Safadi that simulates the patient–ventilator interactions with common modes of ventilation. Similar to the Microsoft Excel script mentioned above, the user can add or remove spontaneous efforts and alter patient features such as compliance, resistance, strength of the patient effort (Pmus), neural drive length, and add a delay to the patient effort to demonstrate all forms of patient–ventilator asynchronies. It has an interactive simulation mode where the waveforms run across the screen as they do

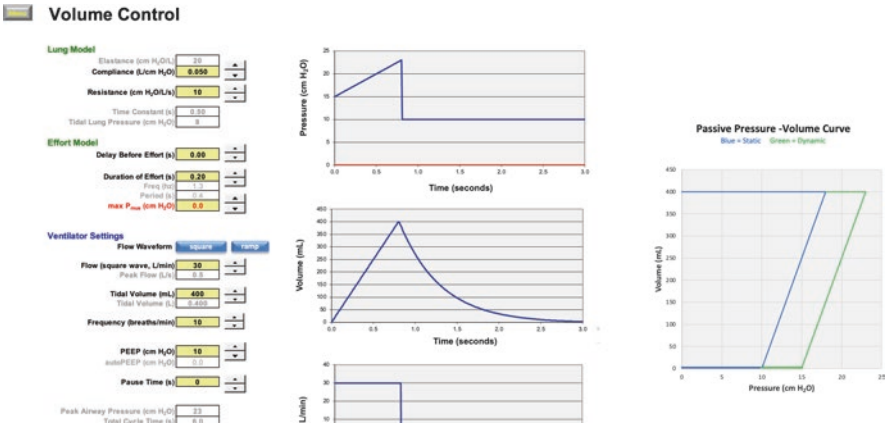

Fig. 37.1 Screenshot of the Simulation Interface for Ventilation Analysis (SIVA) excel file developed by Robert L. Chatburn, MHHS, RRT-NPS, FAARC

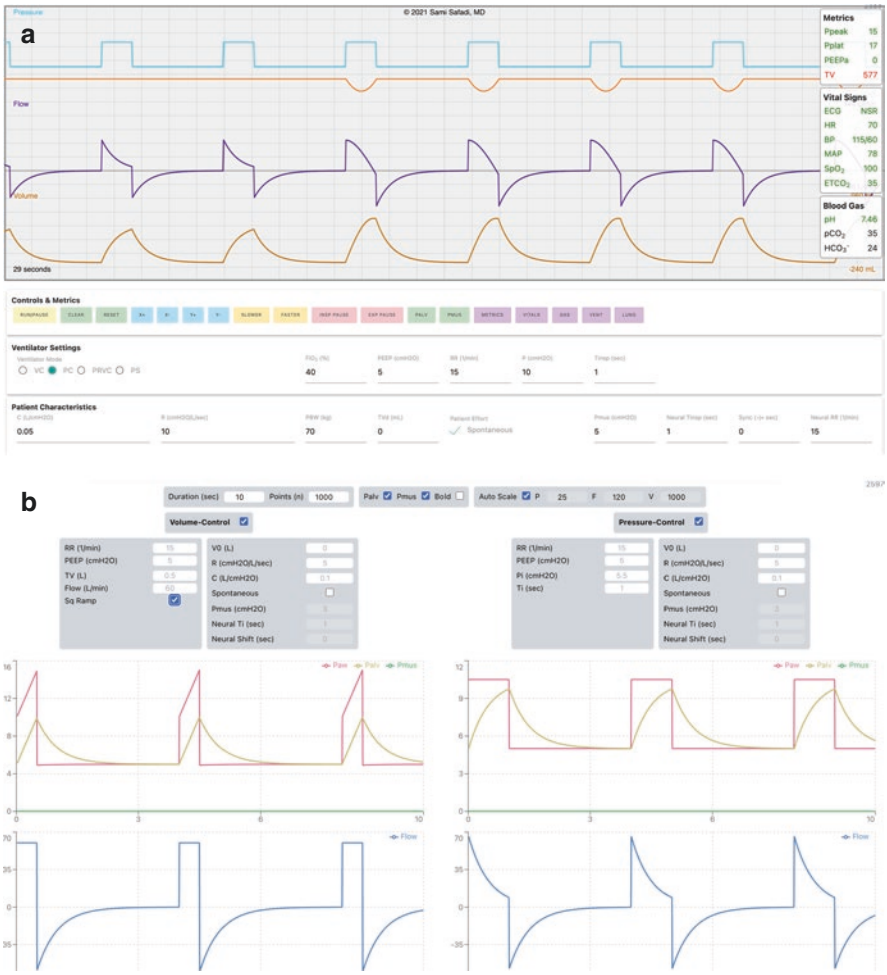

Fig. 37.2 (**a**) Screenshot of the interactive section of the VentSim online software. (**b**) Screenshot of the comparison screen of the VentSim online software

on a ventilator (Fig. 37.2a), and there are other graphical features such as pressure–volume and flow–volume loops, and static waveform analysis of modes, including a side-by-side comparison feature (Fig. 37.2b). The interactive simulator has the ability to increase dead-space tidal volume which will demonstrate a change in the patient's acid-base status, and subsequently responds to ventilator adjustments to respiratory rate and tidal volume. VentSim is free to use but you need to signup and an email verification is required. More information and signup information can be found at https://ventsim.cc (last accessed February 2022).

37.3.1.3 XLung

The XLung is online simulation software designed by Dr. Marcelo Alcantara Holand from Brazil. The simulator has a large selection of modes, and full control over all settings including patient characteristics and effort. There are a number of presets available and physiological parameters such as dead-space and shunt that can be adjusted, and blood gases on screen that change in response to adjusting the ventilator settings including respiratory rate, tidal volume, and PEEP (Fig. 37.3a). After setting up a simulation example, the settings can be exported to use at another time which makes it a great resource for educators. There is a full graphical display to display adjustments in visual waveforms (Fig. 37.3b). The simulator is free to try but requires a subscription for ongoing use and to access all features. The website also has resources and information including video lectures that can be viewed online at no cost. https://xlung.net/en (last accessed August 2022).

37.3.2 Hardware Simulation Options

37.3.2.1 Test Lungs and Breathing Simulators

Simulating mechanical ventilation with a physical (rather than virtual) mechanical ventilator requires equipment to simulate the lungs of the patient, and the ability to control patient breathing patterns is often required. In some cases, the teaching or simulation purpose may not require assessment of patient effort. Test lungs that simply connect to a ventilator circuit, have an inflatable material enclosed on either side with rigid plastic to simulate the chest wall to facilitate passive exhalation. For teaching purposes, test lungs with adjustable compliance and resistance should be preferred if changes in respiratory system mechanics are to be demonstrated. However, if the purpose of simulation is to demonstrate the full patient–ventilator interaction, the breathing simulation equipment and software is needed. IngMar Medical (Pittsburgh, PA, USA) is a popular manufacturer of test lungs and hardware simulation options. They manufacture simple test lungs with adjustable resistance and compliance as well as the most common advanced breathing simulator; the ASL5000. The ASL5000 includes the hardware and software required to run complex simulation sessions. Clinical scenarios can be created and saved, or modified in real time. Another popular manufacturer of lung simulators is neosim AG (Chur, Switzerland). They also have a variety of mannequin options available for simulation.

To create online resources with the above hardware, devices that capture video can be used to record the video output of any ventilator.

37.3.3 Setting Up a Successful Simulation Teaching Event

Adding simulation sessions to an educational event implies that there is an overarching goal that the attendee is expected to learn a technique or action required to

Fig. 37.3 (**a**) Screenshot of the XLung simulation software demonstrating adjustable patient and ventilator settings. (**b**) Screenshot of the XLung simulation software ventilator waveform graphics

manage or respond to a clinical scenario that is being simulated. This normally requires a general understanding or introduction to not only the clinical case or scenario, but also some background information related to why the topic is of concern. Mechanical ventilation courses or events that utilize simulation sessions for teaching can begin with a conference style introduction that follows a traditional structure of answering the "*what*", "*why*", "*when*" series of questions through presentations. For example, if a simulation session was to discuss the asynchrony known as ineffective efforts, a structured approach to education would first answer *what* are ineffective efforts, *why* are they important to the clinical course of a patient, *when* are they most common. The simulation part of the event can continue with a case scenario that presents *who* a patient is (clinical presentation, past medical history, current issues, etc.), and then engage the audience in visual examples through simulation on *how* to recognize and/or correct the issue as it is presented.

While having an actual mechanical ventilator is not required (other options previously mentioned may suffice), having actual equipment is often ideal. Equipment manufacturers are often willing to provide equipment (such as a ventilator) as this may allow new people to experience their product. However, the hardware equipment required to simulate breathing, or project it on to a larger screen for all audience members to see may require additional resources not available through equipment vendors. Ventilation research labs often have lung simulators, and are often excellent resources to have participating in your teaching event.

For audience members to get the most value, you should allow them the opportunity to recognize and interpret the findings presented through simulation, as well as suggest the required changes based on what they've learned. This is followed by performing the suggestions, seeing the results and offering feedback on their choices, whether they are correct or incorrect. When using an actual ventilator, for large groups it may be ideal for time management to perform the suggested changes on behalf of the audience. For smaller groups, allowing them to manipulate the ventilator would be ideal. When using software simulation options (computer screens but not ventilators), the experience of changing numbers with a keyboard or dragging a mouse cursor across a computer screen is not the same clinical experience you are trying to simulate, so audience manipulation will not provide the same benefits, and therefore is not necessary.

37.4 Summary

Teaching mechanical ventilation is best done through introduction of the functional aspects of mechanical ventilators and the various settings available, which can mostly be done in written format. To gain experience in mechanical ventilation and to learn how to manage more complex scenarios and patient characteristics, real-world experience is excellent, but a wide variety of complex clinical scenarios are less common to see and gain expertise. To teach the full spectrum of patient–ventilator interactions, simulation with clinical scenarios is often utilized, and has become an increasingly common form of education.

Vignettes: Controlled Mechanical Ventilation

38

Matteo Pozzi, Giacomo Bellani, and Emanuele Rezoagli

38.1 Introduction

In the following two chapters ("Controlled modes of mechanical ventilation" and "Assisted modes of mechanical ventilation") we collected 24 clinical vignettes representing some figurative examples of two main clinical circumstances that physicians may face up in their daily clinical practice in the Intensive Care Unit about the ventilation management.

Aims of these chapters are to provide straightforward suggestions to critical care physicians on how to:

1. interpret the ventilator waveforms changes at bedside; and,
2. provide available information on how to optimize mechanical ventilation and patient–ventilator interaction in both passively and actively ventilated patients.

38.2 Clinical Vignettes

As first, we here represent ten ventilator conditions under controlled modes of ventilation; we described how to interpret and improve the ventilator setting and monitoring in order to optimize the mechanical ventilation. The described settings

M. Pozzi · G. Bellani · E. Rezoagli (✉)
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy
e-mail: emanuele.rezoagli@unimib.it

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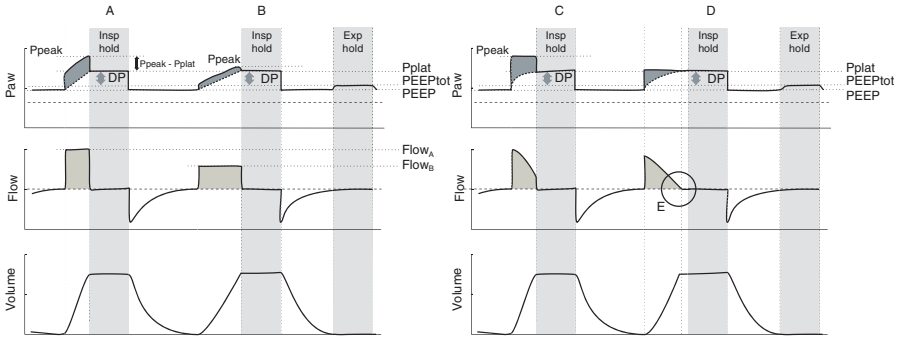
include ventilator conditions during controlled mechanical ventilation in volume and pressure-controlled mode; different modalities of lung monitoring including esophageal pressure measurement and pressure–volume loops; furthermore we reported novel proposed approaches to better understand mechanical ventilation in critical patients, such as the concept of airway closure, the recruitment to inflation ratio and the detection of lung overdistension at bedside by using chest compression.

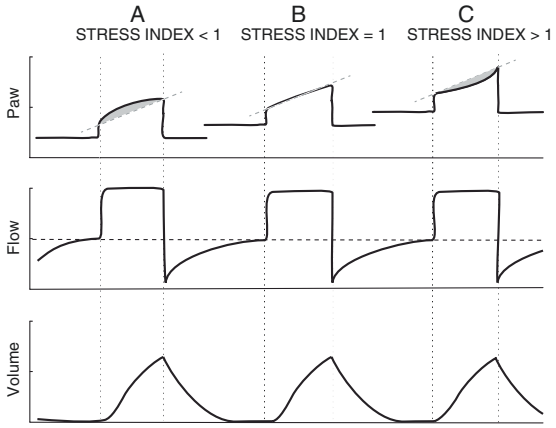
Clinical Vignette 38.1. Measurements of Airway Driving Pressure and Resistance in Volume and Pressure-Controlled Mechanical Ventilation Driving pressure is the elastic pressure distending the lungs and the chest wall when tidal volume is set in volume-controlled mechanical ventilation [1]. Driving pressure is calculated as the difference between the plateau pressure—measured by an inspiratory occlusion maneuver, as expressed by the left gray area in panel A and B—and the total positive end expiratory pressure (PEEPtot)—measured by an expiratory occlusion maneuver—as depicted in the dark gray area on the right side of the figures. The airway resistance is calculated as the difference between peak (Ppeak) and plateau (Pplat) pressure divided by the inspiratory flow. In panel B, despite the same airway resistance as compared to A, the difference between Ppeak and PPlat is visibly different with a greater value in panel A, due to higher inspiratory flow.

The measurement of driving pressure is performed, similarly, in pressure-controlled mode. In panel C and panel D, despite the same driving pressure, airway resistance [2] is different with a greater value and a greater peak inspiratory flow in panel C compared to panel D. In E, it is shown that the inspiratory gas flow goes to zero, meaning that the elastic recoil pressure has equalized the inspiratory airway pressure. Paw=airway pressure; Insp=inspiratory; Exp=expiratory.

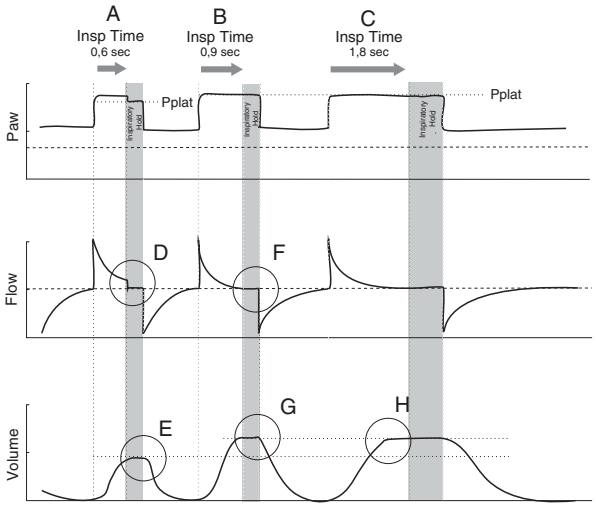


Clinical Vignette 38.2. Stress Index During Volume-Controlled Ventilation The shape of the pressure curve over time in volume-controlled ventilation can be fitted with the formula Paw = $a * t^b + c$. The exponent b is called stress index and may help to tailor lung protective ventilation strategies in ARDS patients [3].

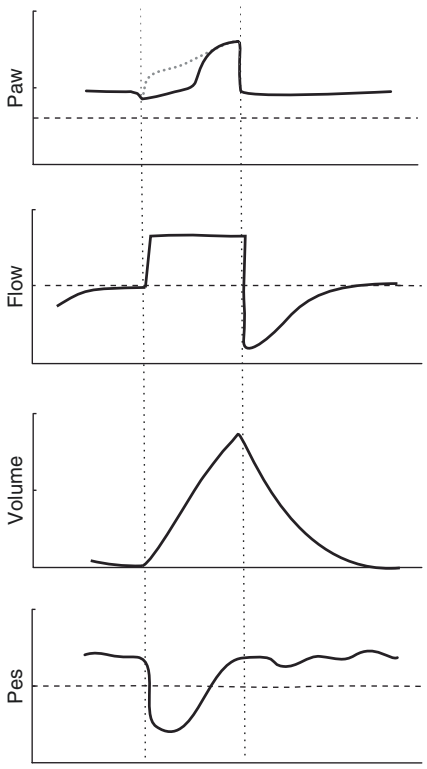
A stress index<1 indicates the potential presence of intra tidal recruitment (panel A). A stress index >1 indicates a potential overdistension (panel C). In the figure, the increase of PEEP allows to move from a stress index <1 (A) to a stress index of 1 (B), which indicates a linear increase of airway pressure over a constant gas flow delivery by the ventilator. A further increase of PEEP may lead to a stress index >1 (C). Some authors advocated for the use of Stress Index as a valuable measure to guide PEEP titration [4]. Paw=airway pressure.



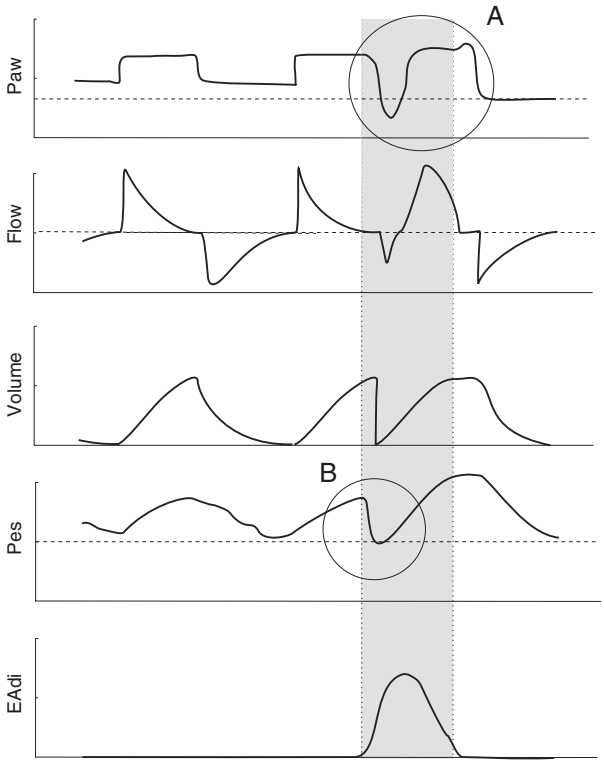
Clinical Vignette 38.3. Pressure-Controlled Ventilation: Effect of Inspiratory Time on Inspiratory Flow Waveforms and Tidal Volume This figure represents typical waveforms of controlled mechanical ventilation in pressure-controlled mode. In panel A, the time of airway pressurization is not enough to equalize the pressure among the airway pressure (Paw) and the alveoli. If an inspiratory hold is performed, airway and alveolar pressure equalize and plateau pressure (Pplat) is revealed. Increasing the inspiratory time allows to zero the inspiratory flow (from D to F) because the pressure at the airway pressure equalizes the alveolar pressure. This leads to an increased tidal volume in panel B as compared to panel A (from E to G). In panel C, there is a further increase of the inspiratory time. However, this does not allow to inflate the lungs further (H) as inspiratory flow already reaches zero. As in panel B, Pplat does not differ from peak pressure and would not require to perform an inspiratory hold (as in Vignette 38.1).



Clinical Vignette 38.4. Ventilatory Asynchronies During Assisted Volume-Controlled Ventilation. Flow Asynchrony This figure represents flow asynchrony. Inspiratory flow is set lower than the patient's demand (i.e., deep deflection in the esophageal pressure, Pes), so the inspiratory airway pressure (Paw) drops as compared to a "passive" breath (dashed line) because the ventilator aims to keep a constant inspiratory flow.



Clinical Vignette 38.5. Ventilatory Asynchronies During Controlled Mechanical Ventilation. Trigger Asynchronies: Reverse Triggering Reverse triggering is the activation of the diaphragm as a consequence of a mandatory breath in controlled mechanical ventilation [5]. As it is seen in the figure, the patient's inspiratory effort (i.e., diaphragm electrical activity, EAdi, and the consequent esophageal pressure swing in the displayed gray area, Pes - B) is generated only after the delivery of a mandatory breath. This means that the patient's inspiratory activation is not triggered by the patient but—in contrast—by the ventilator, from which the word "reverse." Paw=airway pressure.



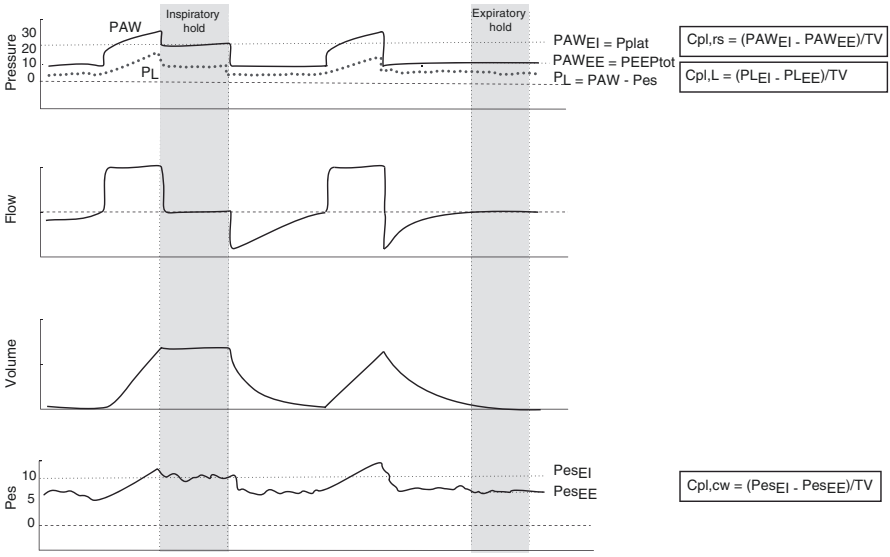
Clinical Vignette 38.6. Transpulmonary Pressure and Measurement of Partitioned Respiratory Compliance During Volume-Controlled Ventilation Changes of esophageal pressure (Pes) are well correlated to the pleural pressure, so esophageal pressure is used as a surrogate to estimate the levels of pleural pressure. The measurement of pleural pressure is relevant as it can provide an estimate of the distending pressure of the lungs (i.e., transpulmonary pressure, PL). The relation between the pressures of the respiratory system is as follows: PL = Airway pressure (PAW) + Pes [6].

As the tidal volume is set in volume-controlled ventilation, the driving pressure distending the lung will be obtained by the difference of the driving pressure of the chest wall from the driving pressure of the respiratory system.

The driving pressure of the airway will be calculated as the difference between the plateau pressure and the total PEEP (PEEPtot), during an inspiratory (i.e., gray area on the left, PAW_{EI}) and expiratory (i.e., gray area on the right, PAW_{EE}) occlusion maneuver, respectively. The compliance of the respiratory system (Cpl,rs) will be then calculated as the ratio between the tidal volume and airway driving pressure (i.e., PAW_{EI}-PAW_{EE}).

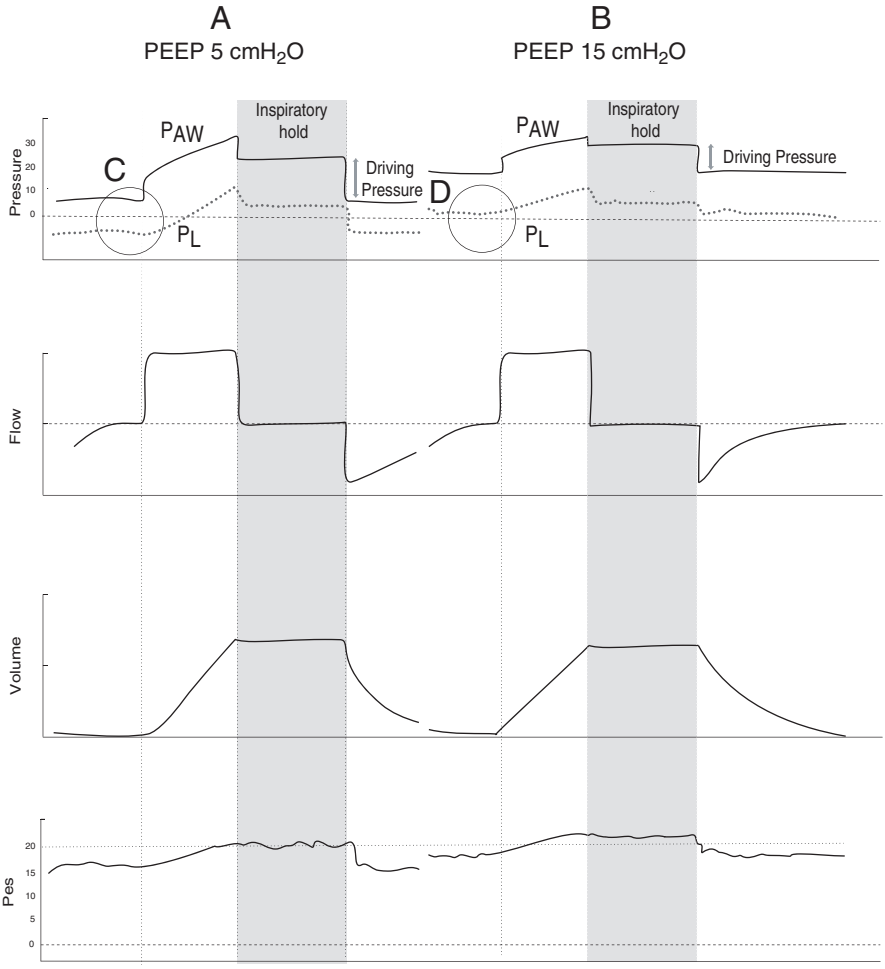
Similarly, the driving pressure distending the chest wall will be calculated as the difference between Pes at the end of the inspiration and at the end of expiration, during an inspiratory (i.e., gray area on the left, Pes_{EI}) and expiratory (i.e., gray area on the right, Pes_{EE}) occlusion maneuver. The compliance of the chest wall (Cpl,cw) will be then calculated as the ratio between tidal volume and chest wall driving pressure (i.e., Pes_{EI}-Pes_{EE}).

The transpulmonary plateau pressure and PEEP will be then calculated as the difference between the airway pressure and Pes during the inspiratory (i.e., PL_{EI}) and expiratory occlusion maneuvers (i.e., PL_{EE}), respectively. The difference between the transpulmonary plateau pressure and PEEP will estimate the transpulmonary driving pressure (i.e., PL_{EI}–PL_{EE}). The compliance of the lung (i.e., transpulmonary compliance, Cpl,L) will be calculated as the ratio between the tidal volume and the transpulmonary driving pressure.



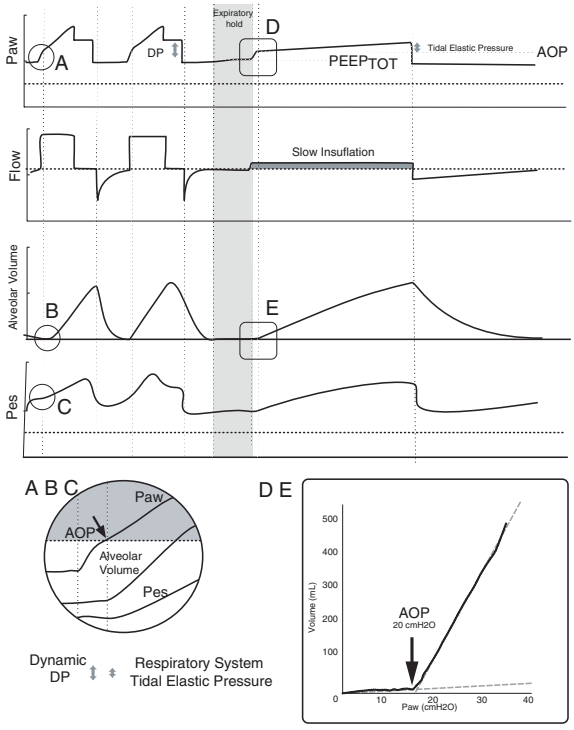
Clinical Vignette 38.7. Effect of Positive End Expiratory Pressure Titration During Volume-Controlled Mechanical Ventilation in Patients with High Pleural Pressure Patients with a high pleural pressure (e.g., obesity) [7] have a right—shifted pressure–volume curve of the chest wall compared to lean sub-

jects [8]. As a consequence, the increase of PEEP (from panel A to panel B) allows to achieve and end-expiratory airway pressure higher than the end expiratory esophageal pressure. Some authors advocate the use of esophageal pressure monitoring during PEEP titration in order to obtain an end-expiratory transpulmonary pressure above 0 cm H_2O [7]. If this approach leads to a significant recruitment of atelectatic areas, it will result in a lower driving pressure.



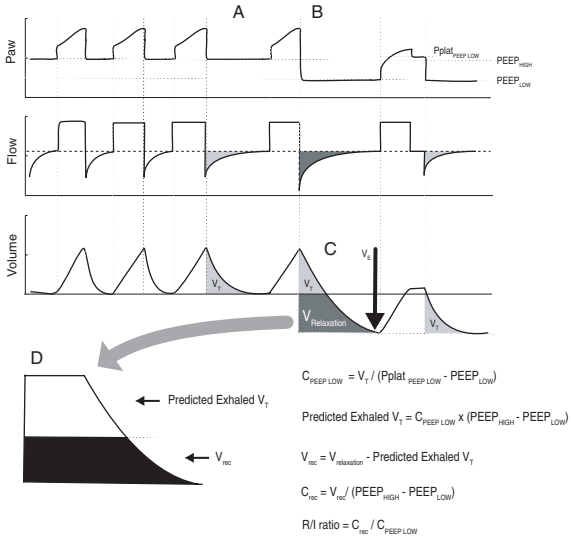
Clinical Vignette 38.8. Airway Closure in Volume-Controlled Mechanical Ventilation This phenomenon was recently described in patients with ARDS as a potential confounder in the assessment of respiratory mechanics [9]. In volume-controlled mechanical ventilation [10], there may be an initial steep increase of pressure (A) in the absence of an inspiratory flow generating tidal volume (B). This

double slope shape of the airway pressure (Paw) characterizes also the initial behavior of the esophageal pressure (Pes) (C). After ruling out the presence of intrinsic PEEP by an expiratory hold, the airway pressure waveform during a slow-flow inflation might unveil the presence of airway closure. Specifically, the change of the slope of airway pressure identifies the "airway opening pressure" (AOP) corresponding to the point from which the gas flow starts to expand the alveoli (D). In the zoomed square on the bottom right, airway closure is identified by the pressure–volume curve of the respiratory system that highlights AOP as the point of change of the alveolar volume generated (i.e., Y axis) over the increasing level of pressure (i.e., X axis) according to the respiratory system compliance. In E, the delay in the increasing volume compared to the starting point of the slow-flow inflation further confirms the presence of airway closure.



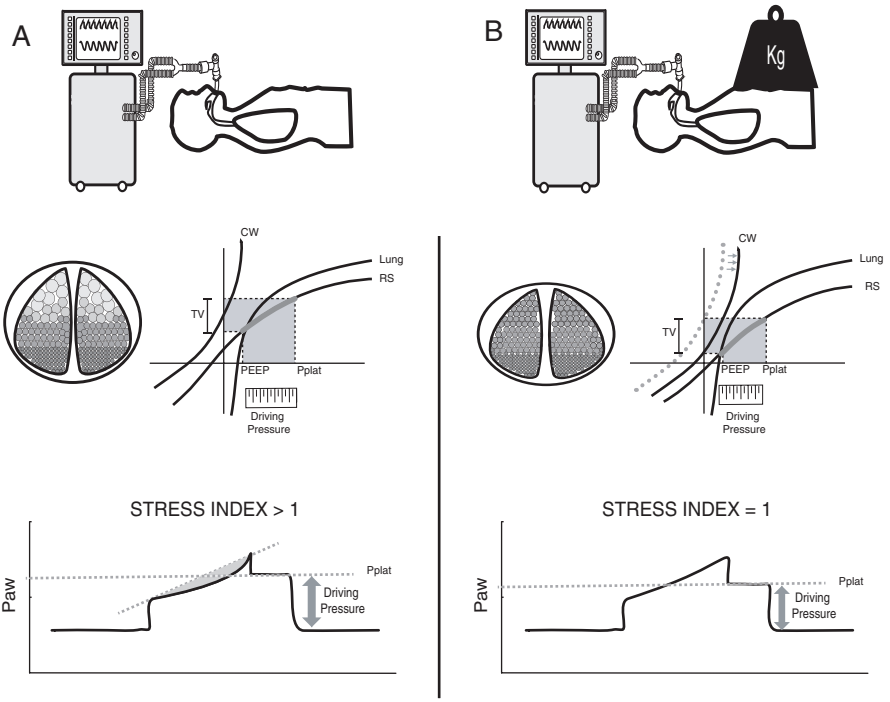
Clinical Vignette 38.9. Recruitment to Inflation Ratio in Volume-Controlled Mechanical Ventilation The quantification of recruitability in patients with ARDS might be of relevance to set PEEP and optimize ventilation. The recruitment-to-inflation ratio has been recently proposed to characterize lung recruitability at the bedside using a single breath method [11]. Two levels of PEEP are defined (i.e., low - PEEPLOW - and high - PEEPHIGH). As first, respiratory rate is decreased in order to avoid the presence of intrinsic positive end-expiratory pressure (A). Then, the overall exhaled volume (VE) obtained after a sudden release of PEEP from the

high to the low side (B) is composed of the set tidal volume (VT) and the relaxation volume (VRelaxation) (C). VRelaxation is the volume obtained by the exhalation from high PEEP (PEEPHIGH) to low PEEP (PEEPLOW). It is composed of the predicted exhaled VT - which can be estimated as the compliance of the respiratory system at PEEPLOW (CPEEPLOW) multiplied by the difference between high and low PEEP (PEEPHIGH-PEEPLOW) - and the recruited volume (Vrec) (D). Vrec normalized by the pressure change (i.e. PEEPHIGH-PEEPLOW) gives the compliance of the recruited volume (Crec). The ratio between Crec and the compliance calculated at low PEEP (i.e. compliance of the respiratory system at PEEPLOW - CPEEPLOW) gives the recruitment-to-inflation (R to I) ratio. In the presence of an airway opening pressure, airway closure must be taken into account into the calculation of the R to I ratio.



Clinical Vignette 38.10. Detection of Nondependent Lung Overdistension by External Chest Compression Mechanical ventilation in ARDS patients aims at reopening the consolidated or poorly aerated lung units while minimizing the risk of lung overdistension in the non-dependent lung areas. Recently, body gravitational changes or the use of external chest or abdominal compressions have been proposed to unveil a paradoxical effect on the respiratory system compliance [12]. As an exemplification of this mechanism, we here report the effect of an external chest compression with a known weight (panel B) on the model of lung CT scan, on the pressure–volume curves of the respiratory system and on the airway pressure waveform of a patient mechanically ventilated in volume-controlled mode and compared to the absence of weight placement on the chest (panel A). The weight positioning decreases the end expiratory lung volume by decreasing the overdistension in the nondependent lung areas. This can be visualized immediately on the ventilator by the decrease of the plateau pressure and

the consequent driving pressure. Furthermore, the stress index—that was >1 before the external chest compression (panel A)—becomes =1 suggesting a restoration of the linear increase of the pressure in the presence of a constant inspiratory gas delivery by the ventilator. The suggested mechanism is a right-shift of the pressure–volume curve of the chest wall (CW) and—consequently—of the entire respiratory system (RS), allowing a tidal ventilation in a steeper part of the pressure–volume curve resulting in a reduced driving pressure under volume-controlled ventilation. This maneuver might suggest the need of decreasing PEEP in the presence of such a response in the decrease of plateau pressure after external chest compression [13]. PEEP: positive end expiratory pressure; Pplat: plateau pressure; TV: tidal volume.



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Vignettes: Assisted Mechanical Ventilation

39

Matteo Pozzi, Giacomo Bellani, and Emanuele Rezoagli

39.1 Introduction

In this chapter, we directed our focus on 14 noninvasive ventilation patterns in spontaneous breathing patients during pressure support or NAVA ventilation; on patient-ventilator asynchronies; and on different modalities of lung monitoring including the electrical activity of the diaphragm.

Clinical Vignette 39.1. Effect of Patient Effort on Inspiratory Flow Shape This figure shows a change in the pattern of the flow waveform in the presence of an increasing inspiratory effort—as seen from A to C by the esophageal pressure (Pes) measurement. Despite an increased esophageal pressure swing, the airway pressure (Paw) does not vary significantly, as expected. In contrast, to achieve the same inspiratory pressure, the ventilator delivers a different inspiratory flow, so that the shape becomes more convex: accordingly, tidal volume increases.

M. Pozzi · G. Bellani · E. Rezoagli (✉)
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy
e-mail: emanuele.rezoagli@unimib.it

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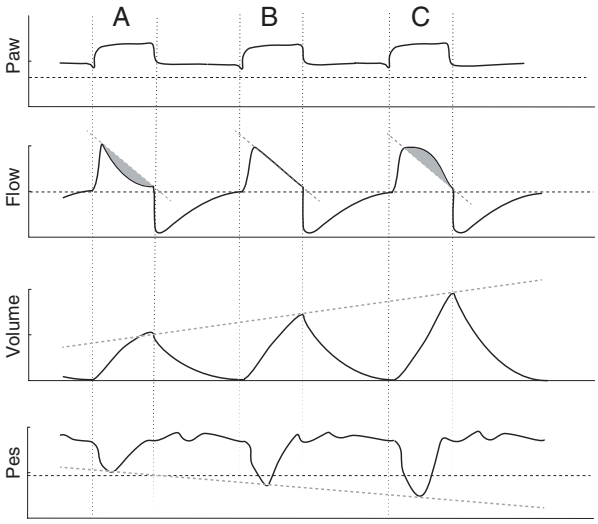
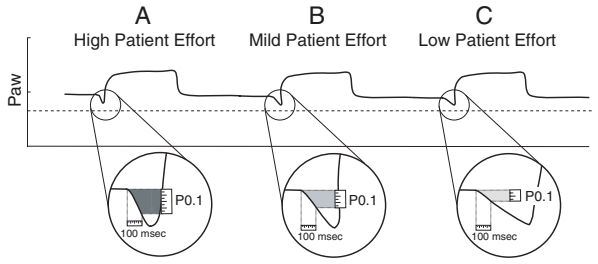
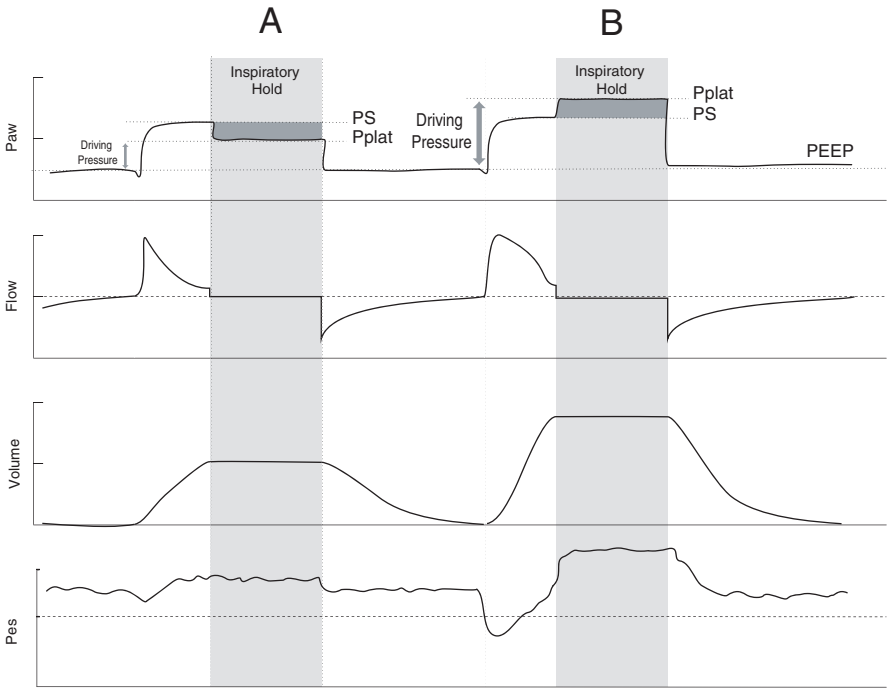


Clinical Vignette 39.2. Monitoring Patient's Inspiratory Effort by P0.1 P0.1—the pressure developed by the patient during the first 100 ms of an inspiratory effort against occluded airways - is a fair estimation of the inspiratory drive in the presence of a ventilated patient with a sealed orotracheal tube and in the absence of sedation or any central neurological impairment [1]. In the presence of a high inspiratory effort, P0.1 will be higher. The slope of the airway pressure (Paw) deflection will be steeper leading to a deeper drop of the airway pressure within the first 100 ms, which is a higher P0.1. If the level of the inspiratory effort is decreased, the P0.1 will be lower. As seen in panel B and C, the slope of the airway pressure will be more gradual leading to a smaller drop of the airway pressure within the first 100 ms, which is a lower P0.1.

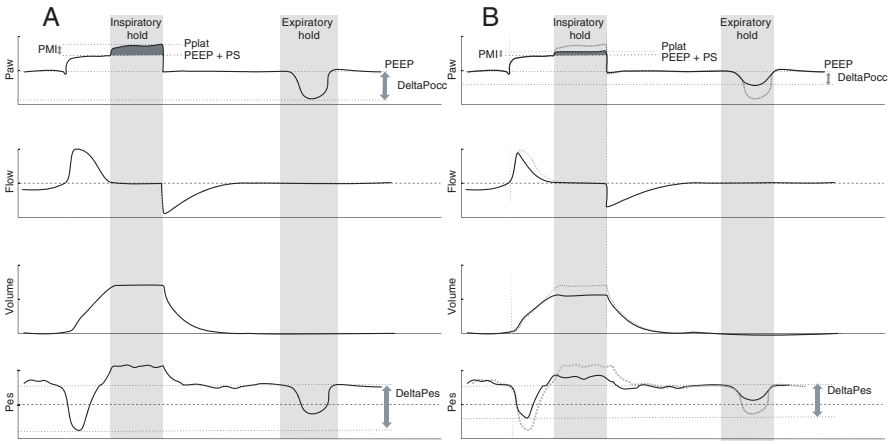


Clinical Vignette 39.3. Measurement of Plateau Pressure and Driving Pressure in Pressure Support Ventilation The figure displays the measurement of plateau pressure (Pplat) during pressure support (PS) ventilation with a low (panel A) or high (panel B) inspiratory effort by the patient. Plateau pressure is measured during an inspiratory hold and it allows the measurement of the driving pressure by subtraction of the total positive end-expiratory pressure (PEEP). In panel A, the inspiratory effort is negligible (i.e. minimal esophageal pressure - Pes - swing) at the end of the inspiration. In contrast, in panel B, patient inspiratory effort is still present at

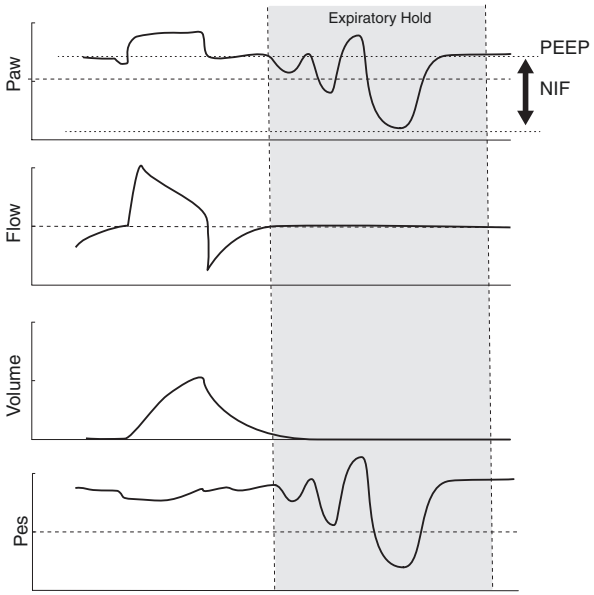
the end of the inspiratory phase (i.e. deep deflection of Pes), so when an occlusion maneuver is performed the plateau pressure is visualized as the pressure support plus the pressure released by the inspiratory muscles at relaxation. The measurement of driving pressure (DP) in both panels is obtained as the difference between the plateau pressure and PEEP [2]. Paw=airway pressure.



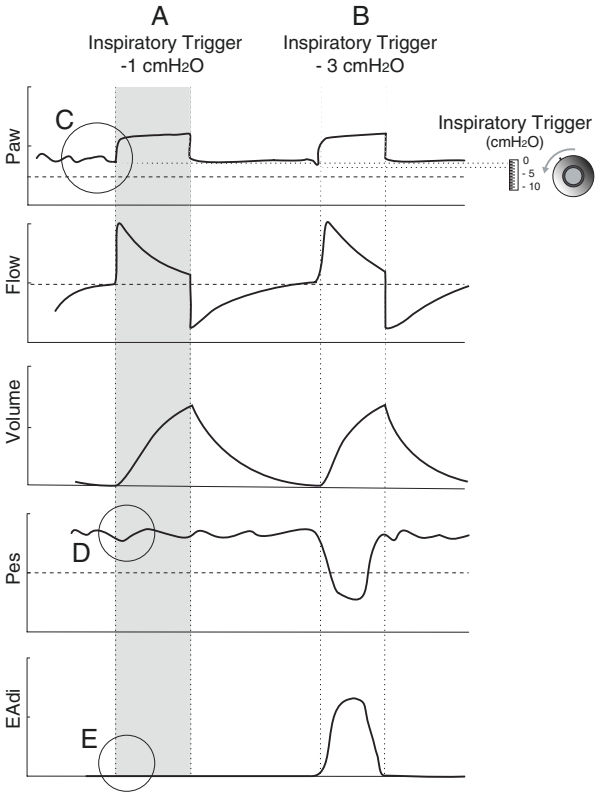
Clinical Vignette 39.4. Quantification of Patient Effort During Pressure Support Ventilation Patient inspiratory effort can be quantified during an inspiratory or an expiratory hold [3]. In panel A, the increased pressure during an inspiratory hold is called Pressure Muscle Index (PMI) and quantifies the inspiratory effort when the subject relaxes the inspiratory muscles. The pressure during the inspiratory hold (gray area on the left side) is the plateau pressure (Pplat) measured in pressure support (PS) ventilation [4]. The pressure measured during the expiratory hold (gray area on the right) is the change of pressure (ΔPocc) that reflects the inspiratory muscle pressure (Pmus) according to the following formula: Pmus = $-2/3$ * ΔPocc [5]. In panel B, we represented the quantification of patient effort by inspiratory and expiratory hold maneuvers in the presence of a lower Pmus as compared to panel A. PEEP=positive end-expiratory pressure.



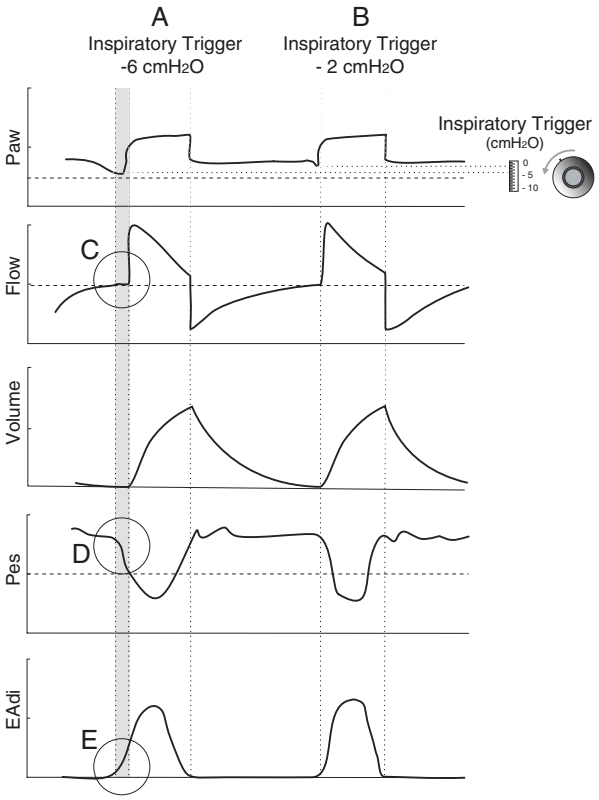
Clinical Vignette 39.5. Measurement of Negative Inspiratory Force (NIF) or Maximum Inspiratory Pressure (MIP) This figure represents the measurements of NIF also known as maximum inspiratory pressure (MIP) [6]. In order to perform this maneuver, the physician must inform the patient before starting an expiratory occlusion maneuver that will last roughly 25–30 s. The patient is requested to perform consecutive inspiratory efforts at the maximal inspiratory generating pressure. The deepest swing of airway pressure (Paw)—or esophageal pressure (Pes)—performed during a prolonged expiratory occlusion maneuver will be considered as the NIF. In the presence of a weaning attempt, NIF values higher than 30 cmH_2O are recommended. PEEP=positive end-expiratory pressure.



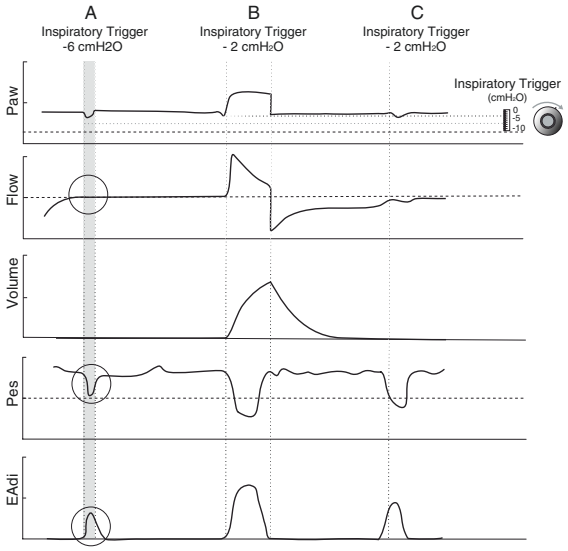
Clinical Vignette 39.6. Ventilatory Asynchronies During Pressure Support Ventilation. Trigger Asynchronies: Auto-triggering This figure represents auto-triggering defined as a ventilator breath triggered in the absence of patient inspiratory effort. In this example auto-triggering (C) can be unveiled by the absence of neural signal (E) (i.e., electrical activity of the diaphragm, EAdi) or of an esophageal pressure (Pes) swing (D). However, a breath was delivered—as seen in panel A—because of an oversensitive inspiratory trigger. Decreasing sensitivity of the inspiratory trigger allowed to avoid the delivery of breaths in the absence of the inspiratory patient's effort (panel B). Paw=airway pressure.



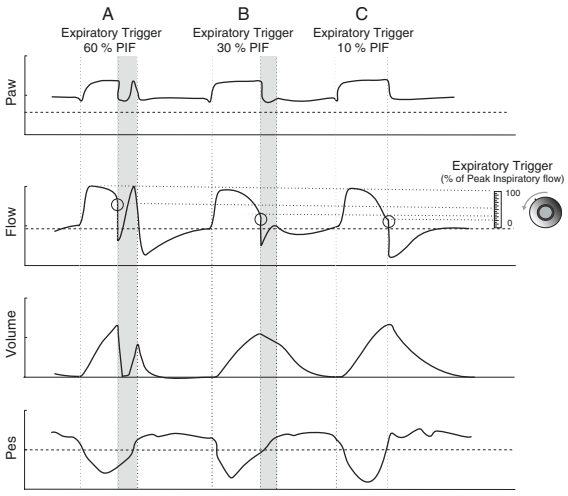
Clinical Vignette 39.7. Ventilatory Asynchronies During Assisted Pressure Support Ventilation. Trigger Asynchronies: Delayed Triggering This figure represents delayed triggering. When the inspiratory trigger is not adequately set, the patient may struggle in developing an effort which may allow the delivery of inspiratory gas flow by the ventilator (panel A). In this scenario, the electrical activity of the diaphragm (EAdi, E) and the esophageal pressure (Pes, D) starts to deflect (i.e., gray area) but the inspiratory flow is not delivered by the ventilator (C). Only when a certain threshold of pressure is reached by the patient's effort (i.e., at least 6 cmH_2O) the inspiratory cycle starts. In panel B, the inspiratory trigger is then lowered to 2 cmH_2O so the inspiratory gas flow can be immediately delivered by the ventilator and matches the patient demand. Paw = airway pressure; EAdi = electrical activity of the diaphragm.



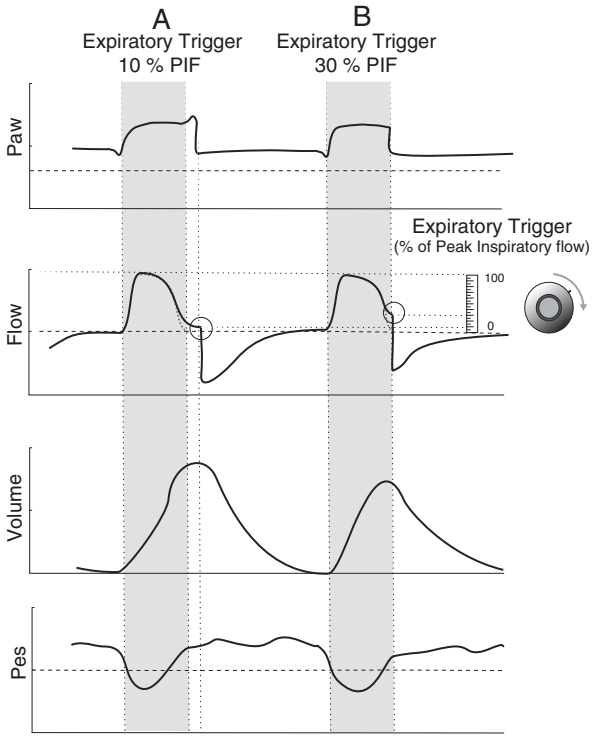
Clinical Vignette 39.8. Ventilatory Asynchronies During Pressure Support Ventilation. Trigger Asynchronies: Ineffective and Missed Effort This figure represents ineffective and missed efforts. If the inspiratory effort is not strong enough to open the inspiratory valve (i.e., gray area), the inspiratory gas flow is not delivered by the ventilator. This typically happens in the presence of an inspiratory trigger set too hard (i.e., -6 cmH_2O, panel A). This asynchrony is commonly called ineffective effort. In panel B, the inspiratory trigger is set at -2 cmH_2O which is a pressure easily achieved by the patient during the inspiratory phase and allows to match the patient demand with the ventilator gas delivery. If the patient's effort starts during the expiratory phase when the flow did not reach zero yet—or in the presence of an intrinsic positive end-expiratory pressure (PEEP) because of dynamic hyperinflation—a new respiratory cycle is not guaranteed by the ventilator, even in the presence of an inspiratory trigger set at -2 cmH_2O. This asynchrony is quite typical of patients with chronic obstructive pulmonary disease who tend to breathe in during the expiratory phase. Paw = airway pressure; Pes = esophageal pressure; EAdi = electrical activity of the diaphragm.



Clinical Vignette 39.9. Ventilatory Asynchronies During Pressure Support Ventilation. Termination Asynchronies: Early Cycling and Double Triggering [7, 8] In panel A, early cycling is followed by double triggering, in the presence of a profound inspiratory effort. Expiratory trigger was set at a high percentage of the peak inspiratory flow (PIF) and the patient was still developing an inspiratory effort strong enough to activate the inspiratory trigger. The negative deflection of the esophageal pressure waveform in the gray area shows that the patient was still in the inspiratory phase of the respiratory cycle. In panel B, the expiratory cycle was lowered at 30% of PIF. Esophageal pressure (Pes) still showed a negative deflection at the start of the expiration that was not sufficient to trigger inspiration, but only reflected in the deflection of the expiratory flow. In panel C, the expiratory trigger was set at 10% of PIF and early cycling was then resolved. Paw=airway pressure.

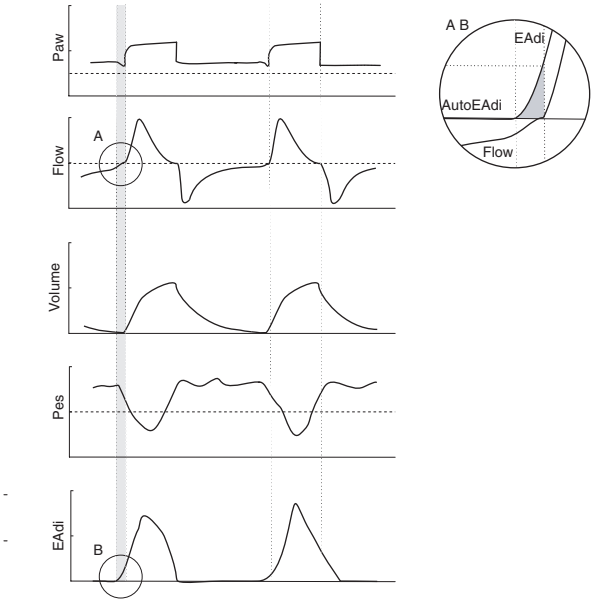


Clinical Vignette 39.10. Ventilatory Asynchronies During Pressure Support Ventilation. Termination Asynchronies: Delayed Cycling This figure represents delayed cycling. Expiratory trigger was set at a low percentage of the peak inspiratory flow (PIF), at which point the patient has already terminated the inspiratory effort—as it can be seen on the esophageal pressure (Pes) (panel A). In panel B, expiratory cycling was then set at a higher percentage of PIF. This synchronized the end of the patient's inspiratory effort and the start of the expiratory phase (i.e., cycling). Paw=airway pressure.

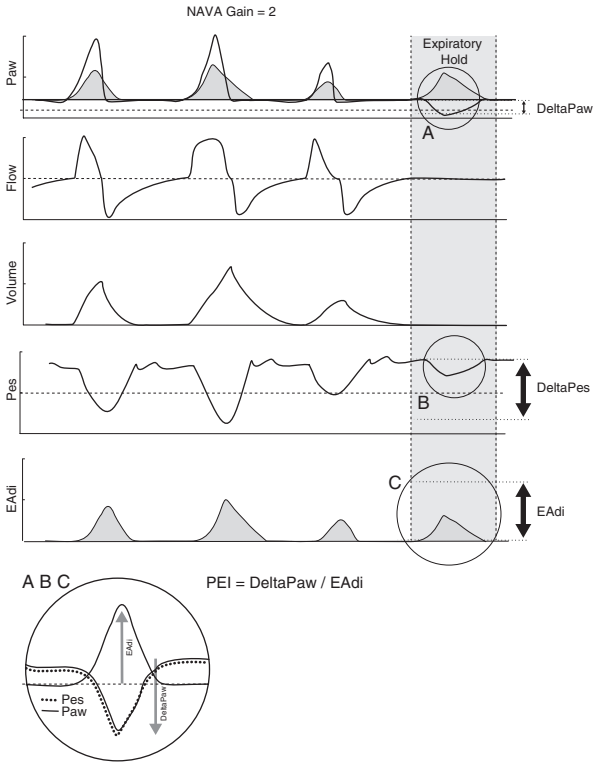


Clinical Vignette 39.11. Measurement of Intrinsic Positive End Expiratory Pressure During Assisted Ventilation In the presence of intrinsic positive end expiratory pressure, an additional effort is required, before starting the inspiratory cycle, in order to overcome it. This can be visualized in the gray area on the left side of the figure as an initial deflection of esophageal pressure (Pes) or of the electrical activity of the diaphragm (EAdi) (autoEAdi) (B) in the absence of inspi-

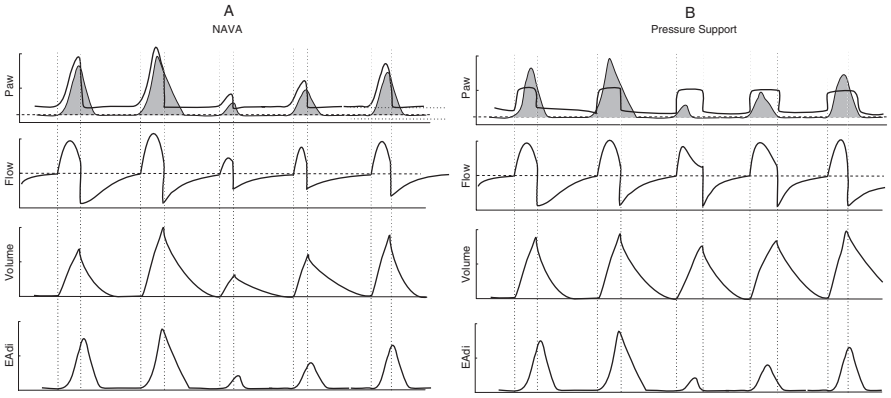
ratory flow (A). The autoEadi (AB) is the electrical activity generated by the diaphragm during the inspiratory phase which is wasted to overcome the expiratory elastic pressure of the respiratory system before opening the inspiratory trigger [9]. Paw=airway pressure.



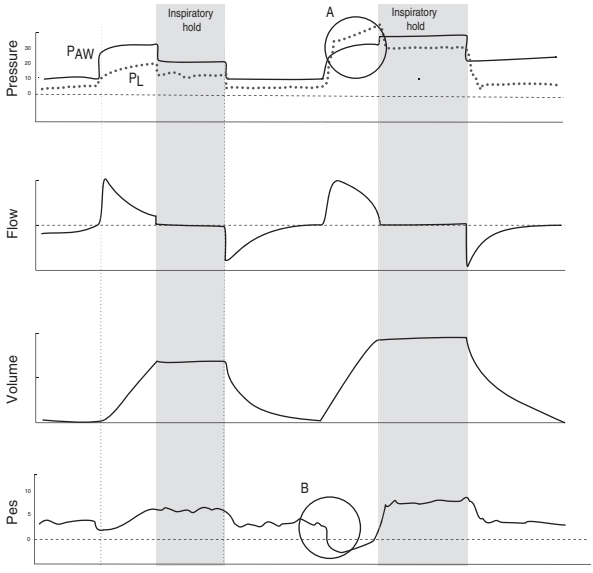
Clinical Vignette 39.12. Neurally Adjusted Ventilatory Assist (NAVA) Ventilation and Quantification of the Neuromechanical Efficiency by the Pressure Pmusc/Eadi Index (PEI) This figure represents Neurally Adjusted Ventilatory Assist (NAVA) ventilation, an assisted mode of ventilation based on the use of the neural trigger of the diaphragm. The signal of the neural activity is expressed in microVolt. The figure shows three different breaths characterized by different patient efforts (i.e., different electrical activity of the diaphragm (EAdi) amplitude) with the same level of assistance (NAVA gain). The shape of the airway pressure is similar to the shape of the electrical activity. Moreover, it is possible to estimate the neuromechanical efficiency of the patient's breathing pattern by the Pmusc/Eadi index (PEI). PEI index represents the coupling between the inspiratory muscle pressure - quantified as the change in airway pressure (DeltaPaw, A) or in esophageal pressure (DeltaPes, B) - that is developed during an expiratory occlusion maneuver and the electrical activity (C) which is necessary to recruit these muscle fibers [10]. The higher the PEI index, the higher is the neuromechanical efficiency. Paw=airway pressure; Pes=esophageal pressure.



Clinical Vignette 39.13. Assisted Modes of Ventilation: Neurally Adjusted Ventilatory Assist (NAVA) Ventilation Versus Pressure Support Ventilation Panel A represents airway pressure (Paw), flow, volume and electrical activity of the diaphragm (Eadi) waveforms during NAVA ventilation. In panel B the same waveforms are represented during pressure support ventilation. During NAVA ventilation, the patient receives a higher or a lower pressure generated by the ventilator in response to a higher or a lower EAdi, respectively. Accordingly, NAVA ventilation is considered a proportional mode of ventilation as the amount of support varies breath by breath based on patient's request (i.e., EAdi). As a consequence, inspiratory flow will vary depending on EAdi (panel A). Conversely, during pressure support ventilation, the pressure delivered by the ventilator is constant in each breath and it does not change despite a different activation of the patient neural activity (i.e., EAdi) and the inspiratory flow will slightly change despite different levels of EAdi (panel B) [11].



Clinical Vignette 39.14. Effect of Inspiratory Effort During Pressure Support Ventilation on the Transpulmonary Pressure This figure represents airway pressure, flow, volume and esophageal pressure (Pes). On the left side of the image, airway pressure (PAW) is depicted. Transpulmonary pressure (PL) is obtained as the difference between Paw and esophageal pressure, which is reported below (i.e., Pes). The gray area represents an inspiratory hold that unveils the plateau measurements of both airway and esophageal pressure, and of the consequent plateau transpulmonary pressure. As the patient's inspiratory effort is mild, plateau transpulmonary pressure is low because the esophageal pressure swing is limited (i.e., left side of the figure). In contrast, on the right side of the figure, the patient's inspiratory effort is more robust than before, as it is seen by the deeper deflection of Pes. As a consequence, the transpulmonary plateau pressure will be higher and may potentially put the lungs at a higher risk of patient self-inflicted lung injury (P-SILI) [12].



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